

IODBASEDOW

THE RESPONSE IN AN IODINE DEFICIENT
POPULATION TO AN INCREASE IN IODINE
CONSUMPTION.

ROGER CONNOLLY, E.D., M.B., B.S.,
M.R.C.P.E.

This Thesis is submitted for the
Degree of Doctor of Medicine
University of Tasmania

June 1972

"Only the man who is familiar with the art and
science of the past is competent to aid in its
progress into the future."

Billroth

C O N T E N T S

	Page
PREFACE	i
INTRODUCTION	ii
SYNOPSIS	iii
1. HISTORY OF GOITRE	1
2. IODINE IN THE ENVIRONMENT	34
3. MODERN GOITRE PROPHYLAXIS	42
4. IODINE IN TASMANIA	52
5. GOITROGENS	63
6. PATHOLOGY OF GOITRE IN TASMANIA	86
7. RELATIONSHIP OF ENDEMIC GOITRE TO CANCER AND THYROTOXICOSIS	109
8. IODINE PROPHYLAXIS IN TASMANIA	124
9. THE CHANGING IODINE ENVIRONMENT	136
10. IODBASEDOW IN TASMANIA	149
11. DISCUSSION	170
REFERENCES	188

PREFACE

Many people have helped in the preparation of this thesis and I wish to thank them all. The cases of thyrotoxicosis and the pathology sections in Southern Tasmania were made available to me by the generous cooperation of all medical practitioners in the area and all hospitals, public and private. Dr. Campbell Duncan supplied many slides, photographed the sections I had chosen, gave me much advice in these matters as well as helping with the geography illustrations. Mr. David Lees produced the many photographs of figures and tables. Mrs. M. Marshall, Miss E. M. Young and Mrs. H. Spencer of the Clinical Library helped a great deal with reference works, obtaining them for me throughout Australia. I am most grateful to my staff in the Department of Nuclear Medicine and Endocrinology who carried out the great number of tests, and to Dr. Peter Davoren of Laboratory Services in Victoria who estimated P.B.I. and urinary iodine concentrations. My colleagues on the State Thyroid Advisory Committee, Professors A. G. Baikie, R.M. Mitchell and B.S. Hetzel, Drs. F.W. Clements, G. Vidor, J.C. Stewart and H.B. Gibson, Mrs. J. Coy and Mr. J. McLaren all gave much needed advice and correction. Dr. G.M. McLeod read the original manuscript, helping with much constructive advice. Professor S. Carey and his staff were a great help in the sections of the work dealing with the geology of Tasmania.

I owe my advisor Professor Baikie a great deal. My wife tolerantly typed and retyped the manuscript and advised me on the layout of the material.

INTRODUCTION

Iodbasedow was the name given to thyrotoxicosis which developed in goitrous people when given extra iodine. Theodore Kocher coined the name in 1909. The sudden apparent increase in the incidence of thyrotoxicosis in Tasmania, in 1966, prompted an investigation into the type of disease presenting, and the environment in which it occurred. The possible relationship of this disease to its environment, with special reference to the future of both was sought.

These matters form the material of the thesis to be presented.

SYNOPSIS OF THE THESIS

Endemic goitre due mainly to iodine deficiency has been recorded in many areas of the world throughout history and its response to crude iodine preparations has been noted. The good effect of the pure element in the treatment of goitre was modified by severe thyrotoxic reactions, reported particularly from areas of endemic goitre.

A rational basis for the use of iodine in prophylaxis against goitre, came with the discoveries linking iodine with thyroid metabolism and measurements of low iodine concentrations in water, soil and plants. Mountainous areas which are far from the sea and have been subjected to glaciation in the last Ice Age are particularly prone to iodine deficiency. The excellent response to iodine prophylaxis in preventing goitre in the children of Ohio, U.S.A. was followed by an equally good one in Switzerland.

However there were further reports of thyrotoxicosis following iodine prophylaxis again occurring in adult goitrous females. It was thought by those who believed that iodine caused thyrotoxicosis in some people, that the size of the dose given was important but examples suggest that this was not so. Indeed many authorities denied the existence of iodbasedow.

Tasmania has been a very satisfactory area to observe these phenomena. Population shifts are minimal and it was a moderately iodine deficient island with a goitre incidence among adult females of approximately 30 per cent. Although goitrogens were pro-

posed as a contributing cause of goitre none such have been found. Iodation of bread gave universal prophylaxis to the population and an excellent response has been achieved. Goitre prevalence in children has fallen to that seen in countries where goitre is not endemic.

The pathology of goitre in Tasmania is similar to that seen in all parts of the world. There does not seem to be any increased incidence of thyroid cancer, cretinism is rare and before iodation of bread the incidence of thyrotoxicosis was lower than that recorded in iodine sufficient communities. Several factors have combined to produce a change in iodine content in the environment of Tasmania, before iodation of bread. The importation of large amounts of food from areas of Australia which are not iodine deficient and the use of iodophors in the food industry provided extra iodine. Several other sources of iodine were brought to Tasmania resulting in a gradual increase in iodine consumption.

A steady increase in the incidence of thyrotoxicosis was noticed from 1960, as shown in Fig. 10-2 with a sudden rise which has continued from 1966 when bread was iodated. It is suggested that the incidence of thyrotoxicosis has risen to that occurring in non-endemic goitre areas, previous iodine deficiency having protected those otherwise prone to develop the disease. If this is so, the incidence will remain similar to that of the average world incidence for non-endemic goitre areas, but the age group affected should become progressively younger.

The addition of iodine to the diet of the population of Tasmania can be justified by the disappearance of goitre and consequent decrease in thyrocardiac disease which is associated with nodular goitre in middle age, the probable disappearance of lethal cancer of the thyroid in the elderly, tracheal obstruction by retrosternal goitre and the cosmetic effect in females who formed the majority affected by the condition.

It is predicted that the price for this will be a slight increase in the incidence of thyrotoxicosis in an age group which will become progressively younger and more able to cope with the disease. On balance at the present time this price is reasonable.

Evidence to support these assumptions are presented in the body of the thesis.

CHAPTER 1

HISTORY

INTRODUCTION.

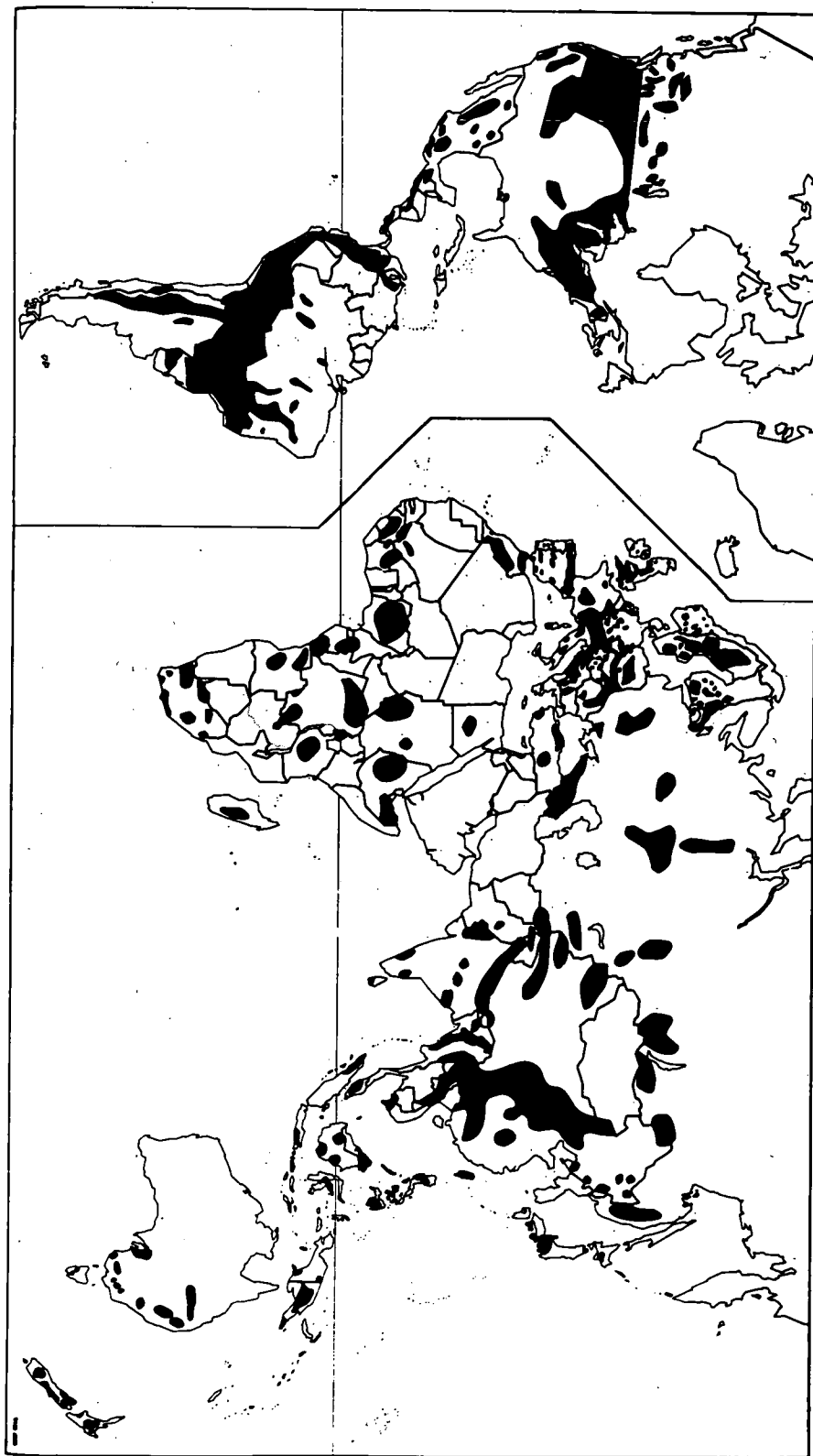
The almost universal prevalence of goitre throughout the world has been recorded in the most ancient sources available and the problems presented by it are recorded in the literature of the Dark and Middle Ages as well as that of the Renaissance. Clear descriptions of myxoedema and cretinism however, were not given until the latter period, and thyrotoxicosis even later in the 19th century. The successful use of crude, iodine containing substances in the treatment of goitre was succeeded in the 19th century by the discovery of elemental iodine itself. Much success followed its empiric use but many cases of toxicity occurred and the method went into disrepute. Meanwhile the theory that iodine deficiency was the main cause of endemic goitre was established, giving reason for its use in prophylaxis and treatment once more. The excellent results obtained by Marine (1916) in schoolchildren in Ohio, U.S.A. encouraged its use but once again iodine given to goitrous adults was associated with thyrotoxicosis. Nevertheless opinion was divided regarding the causal role of iodine in this condition.

Kelly and Sneddon (1960) write as follows "Goitre.. occurs with varying intensity in almost every country.. The disease has been observed in the far north, in the tropics, and in the far south; it occurs independently of climate, season or weather. Moreover, in its incidence goitre makes no distinction of race, nationality, colour, creed or class; the North American,

PLATE 1 - 1

AREAS OF SEVERE IODINE DEFICIENCY
THROUGHOUT THE WORLD

(KELLY AND SNEDDEN 1960)



the European, the Chinese, the Himalayan Indian, the Turkoman, and the peoples of Central and South America all suffer from it under certain conditions -- some severely, some moderately, some but mildly." (Plate 1-1). The empirical use of substances containing iodine and goitre for which it was used, are recorded in very ancient writings.

THE FAR EAST

Goitres were known and described in China in the 8th century B.C. Water, mountainous areas and deep mental emotions are mentioned repeatedly as causal agents in successive writings. The use of the sea weed Sargassum as a treatment for goitre was mentioned by the emperor Shen Ming (2838-2698 B.C.) and repeated in writings down the centuries. The use of deer thyroid is recorded as a treatment for goitre in the book Shen-Shi-Fan written between 420 and 501 A.D. Endemic Goitre and cretinism were recorded by Marco Polo in Yarkand, Kashgar and Chinese Turkestan. In India some authorities suggest that goitre was known from 2000 B.C. but Greenwald disputes this (Langer 1960, Lu Cwei-Djen 1967, Major 1954, Klavin undated, Bornhauser 1936, Greenwald 1949).

NEAR EAST

Little is recorded in ancient Egyptian writings of goitre and its treatment. Some authorities deny the existence of the condition. In the Ptolemaic period fullness of the neck was considered a sign of beauty and became an artistic convention in the time of Cleopatra. In Greece, Hippocrates regarded

drinking water as a cause of goitre and recommended burnt seaweed as a cure (Wilke 1936, Hippocrates 400 B.C. approx).

ROMAN EMPIRE

Vitruvius an architect in the 1st century B.C. writes "The Aequi in Italy and the Medulli in the Alps have a kind of water from drinking which they get a swelling in the neck". Juvenal in the 1st century A.D. writes "who wonders at a swelling of the neck in the Alps?" Pliny the Elder at about the same time states that "Swelling of the throat occurs only in men and swine caused mostly by the water they drink." Celsus (25 B.C. - 45 A.D.) described goitre and recommended surgical removal of the gland but did not carry it out. He did recommend incision of large cystic swellings of the thyroid in order to drain them, at the same time warning about severe haemorrhage from the gland. Water as a cause of Alpine goitre, was once again suggested by Ulpianus in the 2nd century A.D. and the recommendation of cure by burnt sea sponge was repeated by Galen (132-200 A.D.) and Oribasius (325-403 A.D.) (Vitruvius 50 B.C., Juvenal 40 A.D., Pliny the Elder 60 A.D., Foote 1954, Hirsch 1960, Garrison 1967).

The first definitive description of the anatomy of the thyroid was given by Galen. Not until many centuries had passed was the fuller description given by Vesalius in 1543. The name thyroid, meaning an oblong shield was given to the gland by Thomas Wharton in 1656. (Garrison 1967, Vesalius 1543, Wharton 1656).

PLATE 1 - 2

PRE COLUMBIAN FIGURE WITH GOITRE

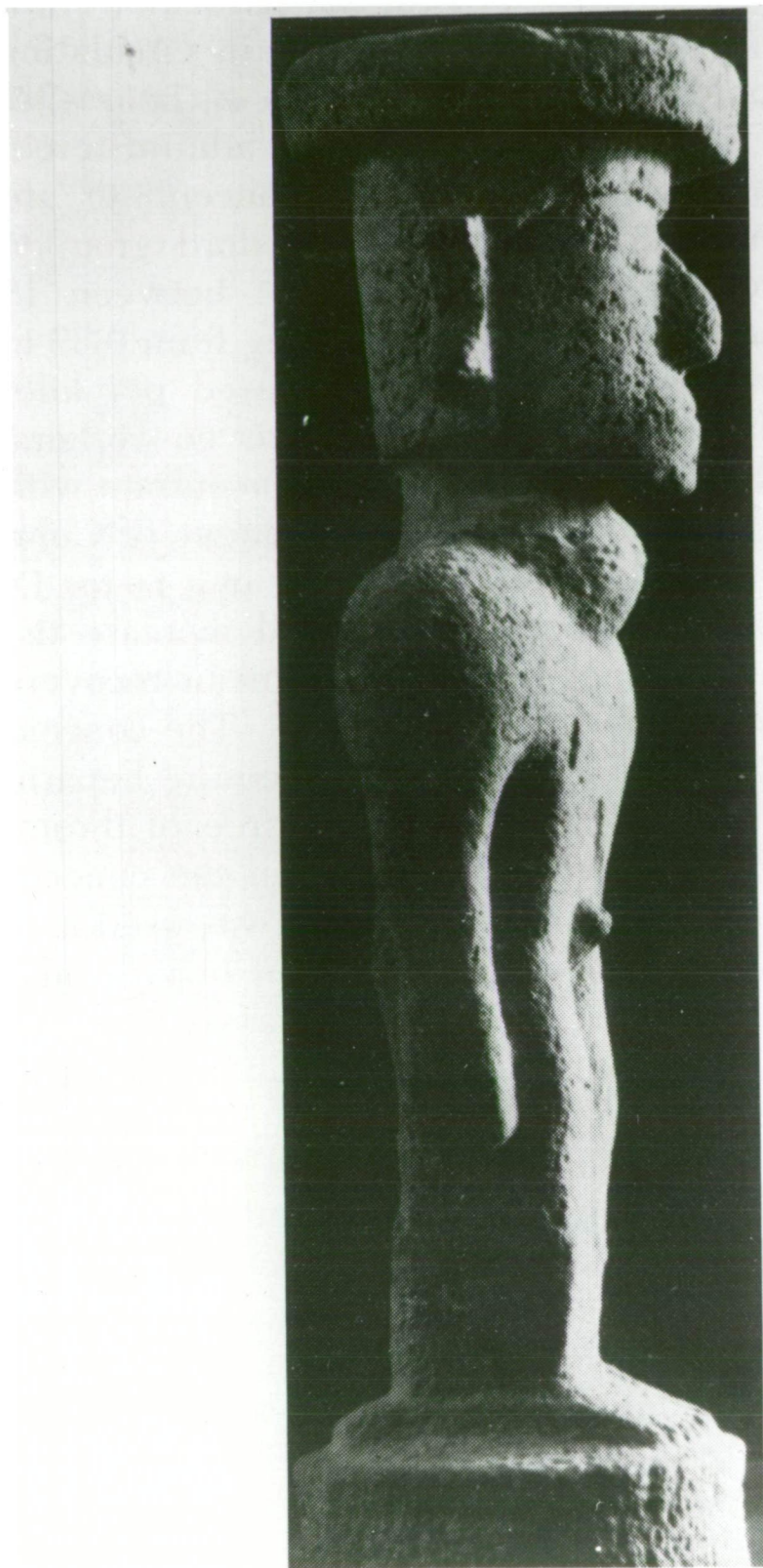


PLATE 1 - 3

GOITROUS CRETIN FIGURINE (19TH CENTURY)
ECUADOR



THE WESTERN HEMISPHERE

There is some record of goitre in South America before Columbus. Perhaps some Mayan and Peruvian statuary show evidence of thyrotoxicosis, but the pictorial evidence produced by Brothwell is not very convincing (Sandison 1967). Nevertheless, in the South American countries that made up the Inca Empire the word "coto" meaning mound or protuberance was used in reference to goitre. These were frequent among the Indians of the Andes at the time the Spaniards arrived (Fierro-Benitez 1969). The recent discovery of a pre-Columbian figure with a prominent goitre, as shown in Plate 1 - 2 testifies to this. The Spanish and their descendents developed goitre after some time in the region. In the 18th and 19th century travellers remarked about widespread goitre amongst both groups and also noted goitrous mentally-defective deaf mute Indians as shown in Plate 1 - 3. As no public health measures of any extent have been carried out in Ecuador, the state of the Indians is judged to be similar to that obtaining at the time of the Spanish conquest. In a recent survey 54 per cent of the population of some Andean villages were goitrous and 10 per cent had neural and motor abnormalities characteristic of cretinism, suggesting that the goitre problem in the Andes has been at least as severe as in the Alps. There is evidence of existing goitre from pottery discovered in Ohio, North America, dating from the mediaeval centuries (Fraser 1962). (Plate 1-4).

PLATE 1 - 4

PIPE FIGURE SHOWING GOITRE

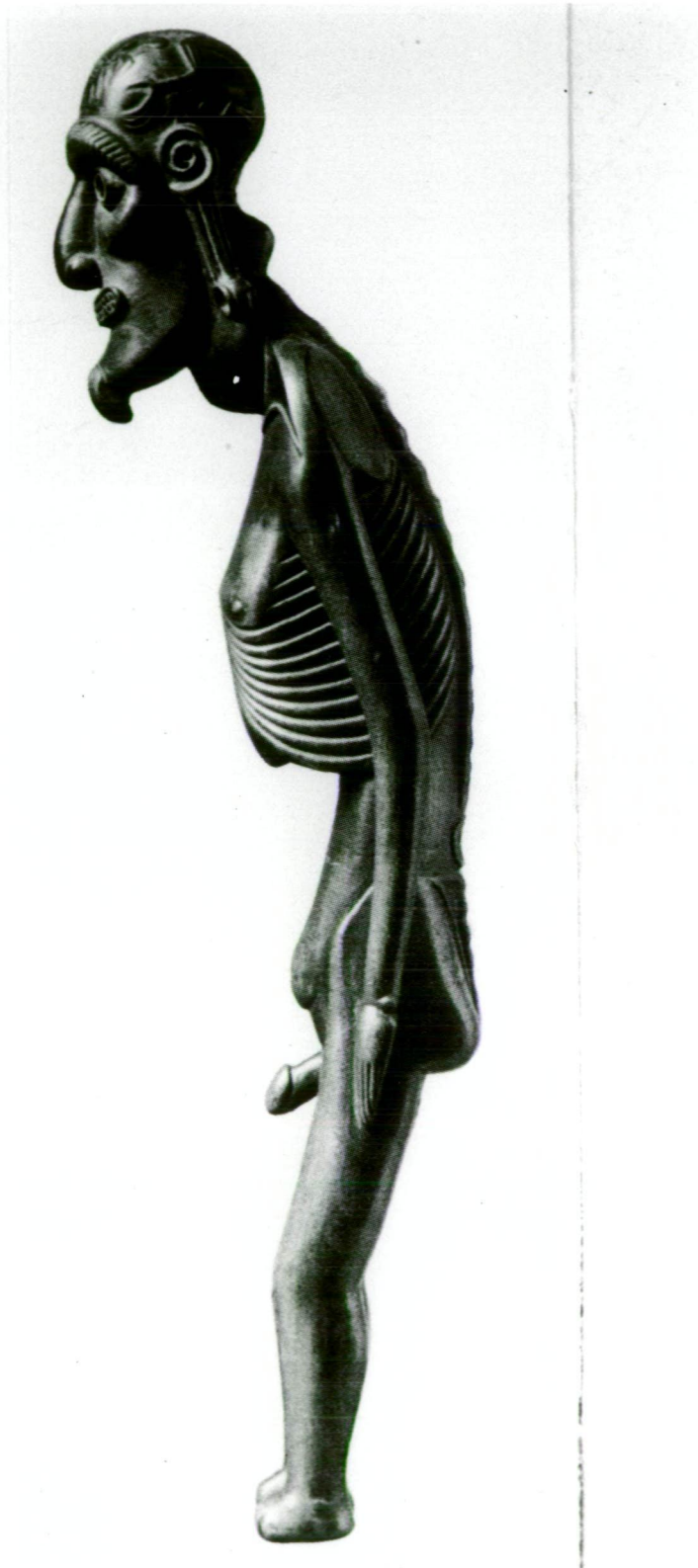
ADENA MOUND, OHIO,
NORTH AMERICA



PLATE 1 - 5

ANCESTOR IMAGE SHOWING GOITRE

EASTER ISLAND, POLYNESIA



THE PACIFIC REGION

Little is known of this area regarding goitre but the charm shown in Plate 1 - 5 from Easter Island depicts a goitrous male (Fraser 1962).

THE DARK AND MIDDLE AGES

Although the rise of Islam brought much new thought in all disciplines there is little record of any work on thyroid disease. It is said that Sayyid Ismail al-Jurjani, a Persian, described exophthalmos with goitre about 1136 A.D. but evidence for this is slender (Rolleston 1936). The Roman systems of medicine were continued in the Dark and early Middle Ages. To these were added superstitious beliefs, one of which was that goitre was a visitation of God and could be cured by the touch of the monarch (Bailey and Bishop 1944).

The School of Salerno in the middle mediaeval period of the 12th century revived the old teaching regarding goitre, and began its extension. One of the great leaders was Roger who suggested two forms of treatment of goitre -- a medical one using seaweed and sea sponge, and a surgical one. For the first time a method of thyroidectomy is described of incision followed by plucking out the goitre with a hook! These medical and surgical treatments were repeated by Gilbertus Anglicus and Bruno da Longoburgo of the School of Padua in the 13th century. The latter stated in his Cirurgia Magna that established goitre could be cured only by surgery (Major 1954). It is interesting that Arnold of Villanova (1235-1312)

advised goitrous Alpine people who were younger than 25 years, to migrate to another region. With the reiteration by Lanfranchi of Milan who died in 1306, that the hard water of the Alps which irrigates the plains of Lombardy was the cause of goitre, it seems certain that thinkers of the time were aware of the connection of mountains, water and goitre. The apparent favourable response of early endemic goitre to water other than Alpine, and the lack of response of long-developed goitre to seaweed and sea sponge was known also. The first mention in history of possible hereditary factors in the development of goitre is given by Guy de Chauliac who was born 1300 A.D. He writes "Goitre is frequently considered to be a local and hereditary disease." (Langer 1960).

The modern workers Matovinovic and Ramalingaswami state that the treatment of goitre with animal thyroid was known in the middle ages in Europe as well as China, but there seems little evidence for this in the descriptions of goitre and myxoedema which were given during the Renaissance (Matovinovic and Ramalingaswami 1960). Dried thyroid for goitre is mentioned in the Persian work Toahf ul Moomineen in 1669 but it may have been in use there in the 14th century (Schelenz 1910). It is apparent that although the influence of some Islamic medicine was felt in Europe, lack of communication was responsible for the large gaps in the transmission of new knowledge from the East.

RENAISSANCE

In 1493 at Einsiedeln in Switzerland, Theophrastus

Bombastus von Hohenheim was born. He was to become the great medical reformer and forward thinker, Paracelsus (Major 1965). After a very restless life he died aged 48 in Salzburg. He was the first to recognise the connection between cretinism and endemic goitre which he described during his time at Basle (Paracelsus, 1603). Five years before the death of Paracelsus, Felix Platter was born at Berne in 1536, and in 1560 he wrote an excellent description of myxoedema (Platter 1560). He became professor of Medicine at Basle, a position he held for 54 years until his death in 1614! Wolfgang Hoefer a Bavarian Court physician at Vienna, was given credit for the first description connecting goitre and myxoedema in 1657, but clearly this had been done by Platter one hundred years before. Hoefer considered the possible causes of goitre and myxoedema in the Alps to be food, upbringing, water and air. He dismissed air, discussed water and wondered if the mercury content of some springs was the cause, but decided that gross eating and laziness due to bad family training were the causes of goitre and myxoedema (Hoefer 1675). An historical fact about which little can be found is mentioned by Garrison. A Malachias Geiger mentions cachexia from overdose of seaweed in the treatment of goitre. Such a remarkable statement is said to have been made in 1636 and if it is correct iodine-induced thyrotoxicosis was described 250 years before Theodor Kocher. No further confirmation can be found nor the amount of seaweed consumed which

PLATE 1 - 6

CALEB HILLIER PARRY 1755 - 1822



produced the cachexia. Geiger was a well known physician in Germany who wrote at least two books on medical topics (Geiger 1636).

DESCRIPTIONS OF THYROTOXICOSIS

Endemic goitre, cretinism and myxoedema had been described but no description of the syndrome associated with excess thyroid function was given until the 19th century. This seems extraordinary when one thinks of the picture of primary thyrotoxicosis presenting now. Credit for the first description of the disease must be given to Caleb Hillier Parry who was born in Gloucestershire England in 1755. He was educated at Edinburgh and became a very successful practitioner at Bath (Major 1965). As a schoolboy he began his lifelong friendship with Jenner who dedicated his original work on smallpox to "C.H.Parry, M.D., at Bath, My Dear Friend." In 1786 he observed the first of eight cases in which enlargement of the thyroid gland was associated with enlargement or palpitation of the heart. These cases, though recorded were not published until 1819 three years before his death, when strokes had forced him to retire from his very busy practice (Parry 1825). The first case in a woman of thirty seven was that of exophthalmos ("the eyes were protruded from their sockets"), with obvious thyrotoxicosis, most symptoms and signs preceding the appearance of thyroid enlargement. The third case occurred in a woman of fifty who "was also long affected with an extremely large swelling of the thyroid gland which began at a period, the relation of which

PLATE 1 - 7

ROBERT JAMES GRAVES 1795 - 1853



to the commencement of the disorder of the heart, she was unable to recollect." The description of the presentation and course of the disease into congestive cardiac failure and death after some years, suggests that she was suffering from toxic nodular goitre. No distinction between these two types of presentation of thyroid disease was made until the further description of secondary thyrotoxicosis by Plummer (Plummer 1913). The other cases described do not allow such a definite decision to be made, and it is interesting that the condition of the eyes is noted in only one of the cases even though four cases whose eye state was not described, were in young women below the age of forty.

In 1800 Flajani in Italy, described a syndrome which could have been that of thyrotoxicosis but it is far from certain that the cases he described, did in fact, have the disease. Nevertheless thyrotoxicosis is called Flajani's disease in some countries (Flajani 1802).

Robert James Graves was born in Dublin in 1795 and died in 1853. In 1834 he described the condition which commonly bears his name in English speaking countries. He published the description in the London Medical and Surgical Journal (Graves 1835). Although Parry described hyperthyroidism before him, Graves description is much more accurately that of primary thyrotoxicosis with exophthalmos. The young female with smooth moderately enlarged gland which showed variability in size over the period of observation, rapid palpitation without cardiac failure or

PLATE 1 - 8

CARL A VON BASEDOW 1799 - 1854



evidence of heart disease, exophthalmos with sclera exposed during sleep, absence of pre-existing goitre are all present in his description. No family history of thyroid disease was given by Graves. Indeed he makes the point that in the cases described no family history of goitre existed. It is a far more complete description of primary thyrotoxicosis than that given by Parry, but his article does not include secondary hyperthyroidism with cardiac failure as in Parry's third case.

The third person to describe this condition without knowledge of the previous two reports was Carl A Von Basedow, who was born in 1799 in Dessau and became a country practitioner in Merseberg in Thuringia (Major 1965). In 1840 he gave a long accurate and detailed history of thyrotoxicosis with all the symptoms and signs (Von Basedow 1840). It appears that one of his three cases may have had malignant exophthalmos and pretibial myxoedema as well as the usual syndrome. After describing primary thyrotoxic symptoms and signs he adds "the legs became from the lower third of the thighs to the extremities, very fat, however not oedematous, the cellular tissue seemed rather brawny..." Although this may not be an exact description of pretibial myxoedema it may well have been the condition. Regarding the eyes "they were pushed out so far that one could see above and below the cornea... could not be closed with every effort. The patient slept with the eyes entirely open. The condition of the Bulbi was not changed, movement towards the side was more

difficult." This is a clear description of exophthalmic ophthalmoplegia but it is interesting that he reported "the vision of the eyes was not influenced in the least and showed only short-sightedness which she had had from childhood". The natural exacerbations and remissions are described, extending over several years. He suggested iodine as a form of treatment for the condition, and was also the first man to describe the autopsy of a case of thyrotoxicosis (Von Basedow 1848).

Thus a disease which may have been present for many years, possibly centuries, remained unnoticed until described by three and possibly four people between 1786 and 1840. Both primary hyperthyroidism and secondary toxic nodular goitre were described, together with malignant exophthalmos and pretibial myxoedema.

IODINE IN THE 19TH CENTURY

The English blockade of the continent of Europe, during the Napoleonic war, forced the French to attempt to extract saltpetre, for their explosives, from the sea. In 1811, during the course of these experiments Bernard Courtois, a native of Dijon, was conducting a series of experiments on ashes of kelp, attempting to extract the mineral substances. He noticed that if sulphuric acid was added to the "mother liquor" violet vapours were produced. Upon condensation these vapours yielded crystalline plates. He was busy with the other portions of the work but passed the information to a friend named Clement, who presented it for him to the Academy of Science

in 1813. Neither Courtois nor Clement suspected the elemental nature of Courtois' discovery, but Sir Humphrey Davy heard of the report, saw the possibility, began experiments which confirmed his suspicion that this indeed was an element. Cuvier, a friend of Sir Humphrey Davy, reported that the latter had announced the discovery of a new element. Davy claimed that the original work on the subject had been done by him. At the same time Gay-Lussac, who also saw the possibility from Clement's paper, completed his work and presented it to the Paris Academy in December 1813. In spite of an unseemly controversy between Davy and Gay-Lussac, Courtois was eventually given recognition as the discoverer. Its name, however, was given by Sir Humphrey Davy from the Greek word ion meaning violet, which in turn is derived from an older word fion, from which the flower violet is derived (La Wall 1926).

With this discovery of iodine from seaweed, Prout began treatment of goitre with iodine in 1816 (Prout 1834). Andrew Fyfe in England, using iodine from sea sponges commenced treatment in 1819 but soon met with difficulty because of its toxic side effects, namely cachexia, cardiac upsets and disturbed menses. Independently of Prout and Fyfe, Coindet and Dumas in Geneva began iodine therapy in 1820 (Coindet 1820). Although most goitres melted with iodine it was soon apparent that toxicity occurred in some cases with tachycardia, dyspnoea, oedema and acute painful swelling of the goitre. At this time they were prescribing 90-180 mgm of iodine daily! Coindet reduced the

dose but in spite of this some patients developed toxic effects. To prevent toxicity he attempted treatment with intermittent dosage. A review by Eggenberger (1938) showed that the dose administered by Coindet was in the region of at least 2000 times the optimum dose.

In 1829 his son Charles Coindet reported favourable results with doses of 10 mgm daily, but iodine remained dangerous in the opinion of most European physicians. Jean Louis Prevost (1790-1850) observed that doses of 0.9 - 2 mgm per day had an effect on goitre, but even this dose produced toxicity in some. However he deduced that the cause of goitre was a deficiency of iodine or bromine in water and prophylactic doses of these substances might prevent the onset of goitre (Prevost 1846). For the first time a theory that the lack of a trace element caused a disease was proposed. This was greeted with much resistance which lasted for almost 100 years. Another concept which took many years to be accepted was formulated at this time. King (1836) first suggested that the thyroid gland acted by the direct secretion of some factor into the blood - internal secretion.

In the meantime Boussingault in Colombia in 1831, had noticed that different population groups suffered from goitre or not, depending on the type of salt they consumed (Boussingault 1833). He found the non goitrous population was using salt enriched with iodine which came from outcrops of rock of differing geological ages. He recommended that iodine be added

to the salt of the other regions. "I consider it certain that goitre would disappear from the Cordilleras if the authorities would take appropriate steps to have established, in the capital of every canton where goitre is endemic, a depot of salt containing iodine whither every inhabitant could go to buy such salt as he required for his consumption." This is the first record of an attempt at large scale treatment with iodine, although Boussingault did not understand that deprivation of iodine was the cause of goitre in the populations affected. His suggestion was not followed. The theory that iodine deficiency was the cause of endemic goitre was first reported by Jean-Louis Prevost and A.C. Maffoni (Prevost 1846). In 1851 Chatin, following investigations of air, soil and water, reported that the incidence of goitre was inversely proportional to the iodine content of the environment. He proposed the prophylaxis of goitre by iodine replacement in 1853 (Chatin 1853). His work was denied by other investigators including Virchow and the idea was dropped.

In 1858 a report on the treatment of goitre with Granger's iodised salt was given to the Academy of Medicine, Paris. This material contained 0.1 G. potassium iodide per kg. i.e. one part of iodine per 13,000 parts of salt ($\frac{I}{NaCl} = 1/13,000$). But Rilliet described four toxic cases analogous to those of Coindet which were produced with much smaller doses. The actual dose of iodide is not stated, but he reported amazement that such small amounts could produce such toxicity (Rilliet 1858). Ricord and

TABLE 1 - 1

SOME CAUSES OF GOITRE

1. WATERS CONTAINING EXCESSIVE QUANTITIES OF:

Suspended matter	Fluoride
Calcium	Barium
Magnesium	Organic matter
Sulphur	Carbonic acid
Gypsum	Volcanic ash
Silica	Coal and metal extractives

2. WATERS DEFICIENT IN:

Oxygen	Phosphate
Iodine	Carbonic acid
Bromine	

3. CONSUMPTION OF:

Vegetables	Fat foods
Milk	Alcohol
Pork	Certain cooking salts

4. CHANGES IN THE ATMOSPHERE:

Humidity	Temperature
Electricity	Sunshine

5. MISCELLANEOUS:

Alcoholism	Consanguinity
Poverty	Unsanitary conditions

THE ETIOLOGY OF GOITRE GIVEN
BY SAINT LAGER IN 1867.

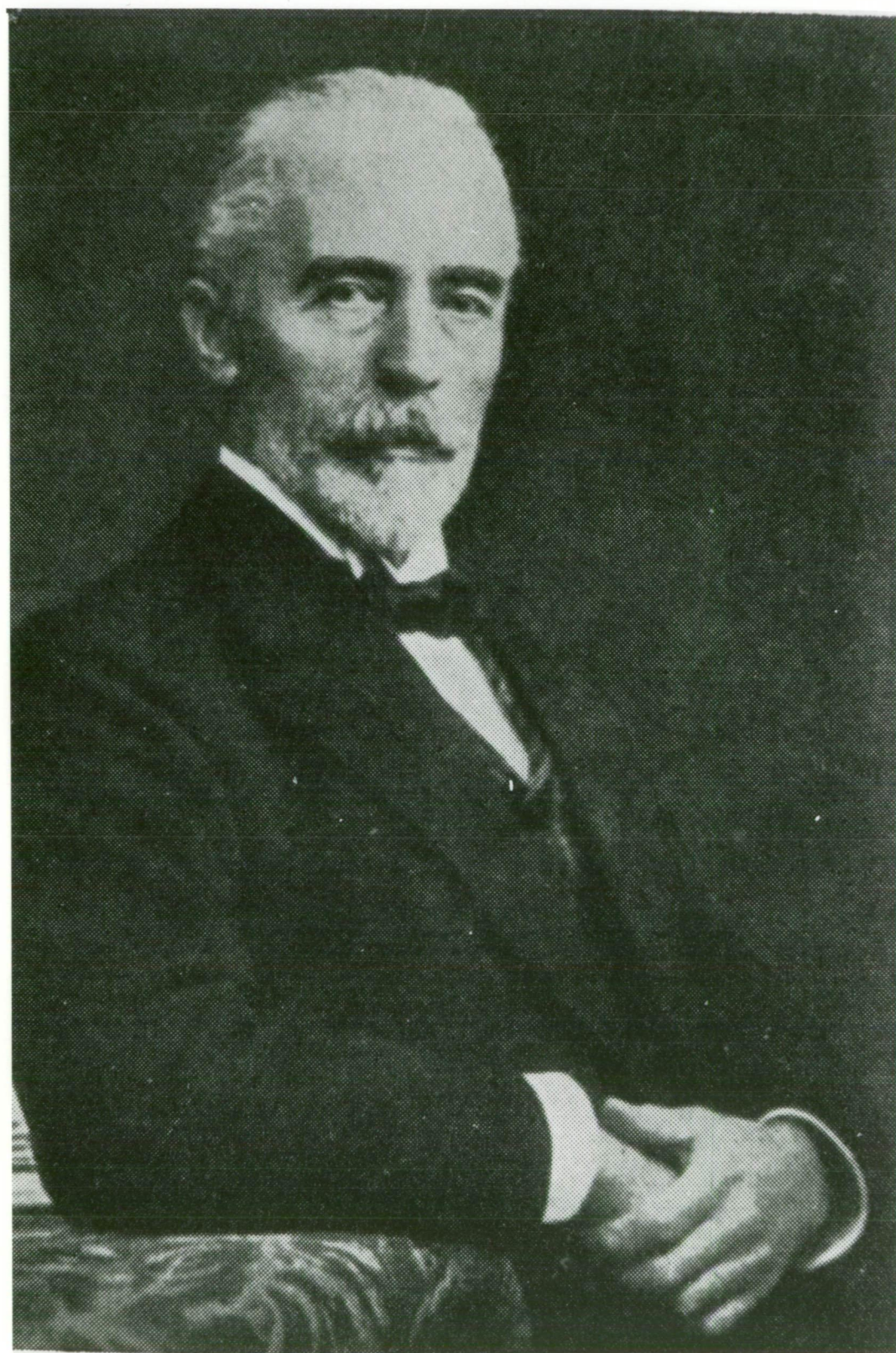
others at this time raised the point that no harm had come to syphilitics who had goitres and had received huge doses of iodides. One attempt to explain these seeming contradictions, was the observation even in Coindets time, that there appeared to be different tolerances to iodine in different regions, e.g. patients in Berlin tolerated doses which were toxic in Geneva. The further extension of this hypothesis, which would suggest that iodine may be harmful to goitrous people living in an iodine deficient area, had to wait another fifty years for the statement by De Quervain quoted later. As evidence of the confusion present at this time Saint-Lager (1867) reviewed the opinions on the causes of goitre. Indeed it would appear that little progress had been made since Hoefer. Saint-Lager found forty three views, the principle ones being shown in Table 1 - 1.

THE INFLUENCE OF KOCHER

In spite of the discovery in 1889 by Eugene Gley, Professor of Physiology at Paris, that the thyroid and blood contained iodine (Garrison 1967), and by Baumann that the thyroid gland contained 10 per cent iodine which he called thyroiodine (Baumann 1896), and the finding of thyroglobulin by Oswald (Oswald 1899) the reaction against treatment of goitre with iodine which began with Fyfe and Coindet and continued with the report of Rilliet, remained. The fear of iodine was increased by the influence of Theodore Kocher who had won the Nobel prize in 1909 for his work in thyroid surgery. In 1910 he coined the name "Iodbasedow", meaning the production of thyrotoxicosis

PLATE 1 - 9

THEODOR KOCHER 1841 - 1917



by iodine in people with preexisting goitre (Kocher 1910). So great was his influence that attempts at prophylaxis with iodide have met with resistance until comparatively recent times. In support of Kocher, De Quervain has said - "Endemic goitre is, so to say, the antagonist of the genuine basedow. To be sure, the latter occur in goitrous districts but all the more seldom, the nearer we approach the endemic centre. It is accordingly more rarely found in Berne than in Basle and affects there not more than one or two per cent of the cases of struma that are operated upon, if we consider only the native patient ... On the other hand endemic struma gives us the great majority of iodine basedow cases. Whereas incredible quantities of iodine can be borne without any thyrotoxic disturbance by most individuals who have normal thyroid glands, with goitre sufferers it frequently happens that daily doses of half to one mgm. of iodine causes iodbasedow to develop which lasts for months if not even for years". Nevertheless he goes on to say "it is also a fact that struma basedowificata produced by iodine (iodbasedow) affects only a small percentage of goitre sufferers who are taking iodine ..." (De Quervain 1927).

In spite of the objections to iodine it seemed to be the only answer at this time to a very serious problem. In Switzerland between the years 1875-81 12,207 young men were rejected from military service because of goitre, and in Italy 1859-64 three per cent of conscripts were rejected for a similar reason (Clark 1921). Surgical removal, with the techniques

available, was not satisfactory because of the large numbers involved (20,000 cases in young men only, in a ten year age group in Switzerland) and the mortality rate of operations being over ten per cent. In 1883, even Kocher reported 30 per cent cachexia strumipriva (myxoedema) following surgery. Although ten years previously Gull had given further descriptions of myxoedema and Moritz Schiff in Geneva in 1856 had shown that dogs who had total thyroidectomy, could be prevented from developing symptoms of myxoedema by the injection or ingestion of thyroid juices (Schiff 1884), no effective replacement therapy was available for humans. The term myxoedema, a term proposed to be applied to an essential condition in a 'cretinoid' affection occasionally observed in middle aged women" (Ord 1878). In 1891 Murray began his classical descriptions of the successful treatment of myxoedema with thyroid extract, followed by Howitz in 1892 with a similar account (Murray 1920, Garrison 1967). Further help in the treatment of goitre came with the work of Kendall (1919) at the Mayo Clinic. He isolated crystalline thyroxine in the years 1915-19. This was followed by the synthesis of the hormone by Harington (1926). It seemed that surgery could not answer the problem without great cost. As a form of mass therapy surgery was physically impossible. Iodine prophylaxis was at least practicable and the ideas of Boussingault and Chatin were revived, in an attempt to prevent goitre developing.

MARINE'S WORK

Between 1909-1913 Marine and Lenhart reported that the development of goitre in brook trout which had almost ruined the fish hatcheries in Pennsylvania, U.S.A., could be prevented by iodine. There appeared to be no untoward effects from iodine on the fish (Marine and Lenhart 1909). It will be remembered that Prevost had suggested iodine deficiency as a cause of goitre almost one hundred years previously, and that it was recorded officially by him and Maffoni in 1846, nearly seventy years before Marine's work. Nevertheless the fact that deficiency of a substance could cause disease was not acceptable to most people at the time. Because of this and Kocher's warning of iodine deficiency it was with some trepidation that Marine gave intermittent iodide to 2000 goitrous schoolgirls in Akron, Ohio, with excellent results. Between 1916-1920 Marine and Kimball reported their results from the same area in 10,000 schoolgirls - 5000 girls received sodium iodide and 5000 acted as controls. Again the dosage was intermittent, the girls receiving four grams of sodium iodide per year, two grams in spring and two grams in autumn each course being given over fourteen days. Before treatment 56 per cent of both groups were found to have goitre. In the treated group no new goitres developed whereas this occurred in eleven per cent of the untreated group. Sixty per cent of goitres present in the treated group regressed during the period of study (Marine and Kimball 1920).

Similar iodine prophylaxis was adopted in Switzerland. In 1918 in the canton of St. Gallen 87.6 per cent of school children had goitre. This was reduced to 13.1 per cent by 1922 following iodine administration. Kimball reports that mild iodism which settled quickly, occurred in eleven children, and no case of exophthalmic hyperthyroidism occurred. Kimball summarised the work of Marine and Lenhart, general experience in Switzerland and his own work as follows:

1. Iodine is necessary for normal thyroid function.
2. The iodine content of the gland varies inversely with the degree of hyperplasia.
3. The percentage of iodine present in individual thyroids is variable but there is a quite constant minimum percentage which is necessary for the maintenance of normal or colloid gland structure (Kimball 1918).

These findings would support Marine's statement "simple goitre is the easiest known disease to prevent". Nevertheless in 1923 although the use of prophylactic iodine in Ohio was increased and some work was being done in Michigan no further extension occurred. It is interesting that every container of iodised salt in U.S.A. carried the poison sign of skull and crossbones, and attempts to force legislation for compulsory iodation of salt for use throughout the community failed.

REACTIONS TO EXCESS IODINE

Some caution however, was sounded in the results of the first experiment in goitre prophylaxis involv-

TABLE 1 - 2

GOITRE PREVALENCE OF AMERICAN
DRAFTEES RELATED TO IODINE
CONTENT OF THEIR HOME
ENVIRONMENT

AREA	GOITRE RATE / 1000	IODINE PARTS/BILLION(U.S.) IN RIVER WATER
1	15 - 30	0 - 0.5
2	5 - 15	0 - 2
3	1 - 5	2 - 9
4	0 - 1	3 - 20

ing all age groups, which was carried out in France in the departments of Bas-Rhin, Seine-Inferieure and Haute Savoie. Goitrous families received iodised salt daily and bottles of elemental iodine were exposed in bedrooms. In this situation with a normal average daily salt consumption De Quervain states "it is small wonder that iodbasedow developed." Cases were frequent and the experiment stopped. These people were receiving between 10 and 20 mgms of iodide per day, a larger dose than that administered by the younger Coindet (De Quervain 1922).

IODINE CONTENT OF THE ENVIRONMENT

Following the work of Bajard in 1919, the Swiss Goitre Commission iodised salt in 1922 in the ratio 5-10 gm. potassium iodide per ton of salt. Work published by McLendon and Williams in 1923 supported this decision, in that they related goitre rate per thousand of draftees into the American Army, with the iodine content of the river water (McLendon and Williams 1923). There was an inverse relationship between the iodine content of the area from which the draftees came, and their goitre rate, shown in Table 1 - 2. McLendon continued this work over many years. Von Fellenberg (1923) who carried out estimates of iodine content in food, soil, rocks and water in Switzerland, Hercus, Benson and Carter (1925) who did similar studies in New Zealand, and Reith (1933) in Holland all showed that goitre rates were inversely proportional to iodine concentration in the environment. The criticism that their methods

were crude and inaccurate may be valid but the important point they made was that the iodine concentrations showed relative deficiencies from one area to the other.

In 1934 about ten years after the introduction of iodide into salt in Switzerland, the prevalence of goitre in children dropped to approximately five per cent but no change in prevalence in pregnancy nor in army recruits was noted. This is not surprising as goitre would have been established in these latter groups before iodine was introduced. It is interesting to recall the advice of the mediaeval surgeon Bruno da Longoburgo and physician Arnold of Villanova in this regard. Their belief that established goitre would not respond to extra iodine in the environment is supported by these observations and the many reports in the literature from areas of moderate iodine deficiency, at the present time. However Richard (1951) reported the result of 27 years (1922-49) of iodide prophylaxis in the cantons of St. Gallen, Thurgau and Appenzell, areas of high endemicity. Goitre prevalence in the newborn fell from 33.3 to 6.8 per cent, and in schoolchildren from 65 to 8.6 per cent. Whereas 67.2 per cent of young men were unfit for military service due to goitre in 1922, this figure had fallen to 0.7 per cent by 1949. This does not seem to be the case in goitres from areas of extreme iodine deficiency where a rapid regression of goitre resulted from the addition of iodine to the diet, as reported from New Guinea (Choufoer and others 1963,

Buttfield and Hetzel 1967), India (Ibbertson 1970), Africa (Delange, Thilly and Ermans 1968) and areas of South America (Scrimshaw and others 1953). A World Health Organisation report of 1960 showed that by 1946 in Switzerland no case of nodular goitre could be found in men under 35 years, and two cases only in women under 40, but this must be treated with some reserve. It will be shown that the carcinoma rate has not altered, and this alone would make for prevalence of thyroid enlargement in the country. (W.H.O. Bulletin 1960).

CHAPTER 2

IODINE IN THE ENVIRONMENT

INTRODUCTION

Since goitre is so widespread and iodine deficiency its main cause, examination of the natural environment occurring in the affected areas is necessary to understand the genesis of the condition.

THE ROCKS

Iodine deficiency in soil and vegetation is widespread throughout the land masses of the world. Many authors have emphasised the effect of recent glaciation in bringing about this state (Sutton 1927). The process removed large volumes of soil entirely, carrying it to the oceans. Replacement of soil by rock weathering has occurred in these areas. Further reduction of iodine concentration has been brought about by the leaching action of heavy snow and rainfall removing iodine through river systems back to the sea. The iodine content of rock of all types is low as shown in Table 2 - 1 (Von Fellenberg and Lündt 1926).

When compared with the average soil iodine, the ratio of rock to soil is approximately one to eight, ratios varying from 1.4 to 35.6 (Von Fellenberg 1926). Even with the lower ratios, the increase in soil iodine concentration from rock would require insoluble iodine compounds which are rarely found in soil, and the removal of incredible amounts of other less soluble rock and soil constituents (Goldschmidt 1954). Until recently, no correlation between endemic goitre, rock type, age and geological formation has been found. Preliminary work by Koutras and others suggests that a high concentration of limestone may be important (Koutras and others 1970).

TABLE 2 - 1

IODINE CONTENT OF ROCK AND SOIL

BASALT	0.20	mgm	per	Kg.
LABRADORITE	0.23	"	"	"
LARVIKITE	0.30	"	"	"
GRANITE	0.20	"	"	"
OBSIDIANITE	0.32	"	"	"
SOIL (AVERAGE)	2.0	"	"	"

TABLE 2 - 2

IODINE CONTENT OF MARINE
VEGETATION AND FISH

BROWN ALGAE	1000 - 7000	mgm	per	Kg.
Laminaria	100 - 1000	"	"	"
Fucus	100 - 1000	"	"	"
Sargassum	100 - 1000	"	"	"
RED ALGAE	10 - 1000	"	"	"
GREEN ALGAE	10 - 1500	"	"	"
SPONGES	1000 - 20,000	"	"	"
FISH (SEA)	1 - 30	"	"	"
FISH (FRESH WATER)	.03 - 1.0	"	"	"

THE SEA

Soil iodine gradually increases by external addition, mainly from the huge iodine stores in the sea. Unlike land vegetation, sea plants and animals concentrate iodine. Some of the concentrating systems are shown in Table 2 - 2, compared with that of fresh water fish (Vinogradov 1959).

The process of iodine replenishment is very slow, requiring hundreds of millennia to produce saturation, in iodine deficient areas. Evaporation from sea water produces iodide which is oxidised to iodine in the air. A similar process occurs in iodide dissolved in fine sea spray. Both are carried many miles by prevailing winds. Yet another method of transport by the wind is the condensation of iodide and iodine solution onto fine dust particles which are carried. Atmospheric iodine and iodide are quickly and thoroughly removed by rain and snow, precipitating it back into the sea or onto land, at random.

Von Fellenberg believed that gaseous iodine formed the main replenishment (Von Fellenberg 1926). McLendon thought that carriage by dust particles was more important (McLendon 1939). Goldschmidt believed that all the possible mechanisms contribute viz. gaseous iodine, iodide and iodine dissolved in sea spray and iodide attached to dust particles (Goldschmidt 1954). If these are the main mechanisms for iodine replacement, variation of them will alter the supply. Thus distance from the ocean, strength of prevailing winds, mountain barriers blocking spray and dust particles, height above sea level, variation in rain

and snowfall, are of importance.

Not all iodine precipitated from the atmosphere goes towards replenishing the deficiency. High rain and snowfall, carrying the iodine to earth, produces large river systems which help to irrigate and add iodine to the soil, over which they flow. But much of this water, containing dissolved atmospheric iodine plus extra amounts leached from the highland areas, flows back to the sea. Thus precipitation, though adding iodine from the atmosphere, may be the cause of a return of iodine to the sea. The net result, depending on variation in the several factors mentioned, could be an overall depletion from the land.

THE SOIL

The soil itself plays a large part in the conservation and availability of iodine. Recent post glacial soil, formed from rock, is poor in iodine and lacking the effect of vegetation for a sufficient time, is porous. Heavy rainfall takes iodine into the subsoil away from the growing surface vegetation and it may not return, unless warmth with evaporation brings it up again. There is an increase in iodine in subterranean water at the expense of the surface. In warm climates a seasonal variation in plant iodine occurs. Evaporation from the surface draws the subterranean water up again by capillary action, bringing its dissolved iodine to the plant root systems.

Highland areas where snow and rainfall are highest are frequently covered by peaty soil. The high content of humic acids in peat binds iodine and prevents its

TABLE 2 - 3

IODINE CONTENT OF WATER

	mcg / litre
SWISS TOWNS	0.2 - 1.5
EUROPEAN RIVER WATER (1926)	0.3 - 5.0
EUROPEAN RIVER WATER (1934)	0.7 - 3.0
12 GREEK VILLAGES (SURFACE)	2.17
14 GREEK VILLAGES (SUBTERRANEAN)	7.0
LEACHED MARINE SEDIMENT	1,000 - 300,000
HOT SPRINGS	2,000
OIL WATER	10.000 - 100,000

(GOLDSCHMIDT 1954).

release to irrigate the pastures on the lower ground. Burkat has shown that humic acids do not bind iodide but actively adsorb iodine. He found that 67 per cent of that adsorbed was bound chemically and could not be eluted (Burkat 1965). Katalymov and others showed that lime had a similar effect, in preventing the uptake of iodine from soil by vegetation (Katalymov and Churbanov 1960). Such high mountainous areas which were subject to glaciation, soil removal and consequent iodine deficiency, tend to perpetuate this state, slowing down the replenishment of the lower land. Thus the porous podzolic soil of the plains is poor in iodine at the growth surface and the peat of the highlands contains increased amounts of iodine, which are not available.

THE WATER

The concentration of this element in water is used as a rough index of iodine nutrition in man. Irrigation, with water of normal concentration, to soil with an adequate basic supply of the element, should guarantee a continuing supply of vegetation, containing normal amounts of iodine. Koutras and others in Greece have shown that this occurs (Koutras and others 1970). An average water concentration of less than 3 mcg/litre was found to be associated with thyroid enlargement by Murray in Great Britain and Koutras in Greece, as well as many others (Murray and others 1948, Koutras and others 1970). Water from all Swiss towns give concentrations from 0.2 - 1.5 mcg/litre (Goldschmidt 1954). If water were the only source of iodine a concentration of 3 mcg/litre would

require the consumption of approximately 30 litres per day to maintain a normal iodine intake. On the other hand subterranean water particularly if associated with limestone can have concentrations up to 30 mcg/litre (Malamos and others 1971). These concentrations of iodine are not confined to subterranean water. Boston water supply has concentrations up to 27 mcg/litre (Stanbury and others 1954). In hot climates with this type of water supply, the daily iodine requirement can be met from drinking water alone. It should be remembered that iodine from limestone is satisfactory when consumed by man and animals but its transfer to vegetation is impeded by the lime. In Europe high concentrations have been found only in subterranean water in Greece. Table 2 - 3 shows iodine concentrations from various sources. The last three examples given in the table are unfit for human consumption and vegetation is not produced from the environment in which they are found.

THE VEGETATION

Unlike marine plants, land vegetation cannot concentrate iodine, although Pauwels has shown that it acts as a micronutrient, increasing growth of many species (Pauwels 1961). Because of this lack of concentrating power, iodine-poor soil produces iodine-poor vegetation. Shulpinov showed that potatoes grown from low iodine soil, contained one thirtieth the iodine of that grown in normal soil (Shulpinov 1957). Butler and others report not only a low uptake from iodine poor soils but even less uptake from some fodder species (Butler and others 1956). Fish

fertiliser or seaweed, either as ash or decomposed organic matter, produces a great increase in the iodine content of vegetables and animal fodder (Gurevich 1962).

CONCLUSION

These then are the various factors which assist and retard man and other animals in obtaining iodine from the environment. A daily intake between 70 and 100 mcg of iodine is necessary for most people if thyroid enlargement is not to occur. In many areas of the world there has not been enough time for the very slow accumulation of iodine to reach a satisfactory level. The reasons for this are given in this chapter and their application specifically to Tasmania in Chapter 4.

CHAPTER 3

MODERN GOITRE PROPHYLAXIS

INTRODUCTION

Various methods of iodine supplementation to the diet in endemic goitre areas are available. Unfortunately iodine induced thyrotoxicosis has been reported following every method of iodine prophylaxis. Nevertheless many workers deny that there is any risk. The size of the dose of iodine does not seem to be an important factor in the production of thyrotoxicosis. There is no doubt however, that environmental iodine deficiency exists in areas of endemic goitre nor is there any denial by any worker of the rare occurrence of myxoedema and cretinism due to excess iodine ingestion.

IODINE SUPPLEMENT TO FOOD

By 1960 the countries in the accompanying Table 3 - 1, had iodised salt available in the concentration shown. Other methods of giving additional iodine have been advocated at various times. Iodination of table salt alone has been criticised by Osmond and Clements in that it was not taken by infants and young children who most need it (Osmond and Clements 1948). Iodised cooking salt may be criticised if it is supplied for home use and not in the manufacture of foods outside the home. Tablets or sweets with added iodide, given at regular intervals, have been used extensively over the past years, but their distribution is dependent on cooperation of parents and teachers which is not always available. These forms of supplementation have never been applied to a whole population. Iodised water is very wasteful in that a very small portion is

TABLE 3 - 1

COUNTRY	IODINE CONCENTRATION IN SALT			
U.S.A.	1	IN	10,000	
CANADA	1	IN	10,000	
AUSTRALIA	1	IN	20,000	
NEW ZEALAND	1	IN	20,000	
ARGENTINA	1	IN	30,000	
SOVIET	1	IN	40,000	
MEXICO	1	IN	66,000	
ENGLAND AND WALES (all NaCl)	1	IN	100,000	
ENGLAND AND WALES (table)	1	IN	40,000	
SWITZERLAND	1	IN	200,000 - 1	IN 100,000
NETHERLANDS	1	IN	100,000	
ITALY	1	IN	100,000	
YUGOSLAVIA	1	IN	100,000	
POLAND	1	IN	200,000	

actually consumed and many areas of endemic goitre do not have a reticulated supply. This last method was employed in Holland where reticulation was confined to the larger towns and many country areas did not receive additional iodine. This method, introduced before the second world war was costly and was terminated when the supply of iodine was cut off in 1941.

In 1943 iodised salt 1/25,000 was used in the baking of bread in Holland and in some goitrous areas, legislation was brought in so that only bread made with this salt could be baked, transported or sold. With this method the average daily consumption of iodine from bread was 100 mcg. This is equivalent to the average daily consumption of 1/100,000 iodised salt, but it enables infants and young children to receive some iodide. This measure, over 8 years, in children 6 to 12 years of age resulted in a total reduction of visible and palpable goitre from 33 per cent to 13 per cent in girls. Where the goitre was previously easily visible (4 per cent in boys and 6.5 per cent in girls), the incidence fell to zero (Pasma 1948). Further modification of this method was made by Hipsley in Australia and such bread has been used in Canberra, the National Capital since 1953 on the recommendation of the National Health and Medical Research Council of Australia (Hipsley 1956). With yet further modification it was introduced throughout Tasmania, an island State of Australia, in 1966. In the last modification iodate is substituted for bromate in Bread improver which is an essential

constituent of modern baked bread. This substance is available to the Tasmanian bread industry through only one distributor, assuring iodation of all bread baked and sold commercially. The excellent results of this procedure were reported by Clements and others (Clements and Gibson 1970). Reduction of goitre in schoolchildren has been similar to the experience reported in Holland.

Beginning in 1961 modification in bread manufacture in the United States of America produced wide variation in the concentration of iodine in this food. In some parts of the country the contribution from this source is negligible but in others relatively huge doses are provided. This effect was not planned and may not continue as bread manufacturers are changing from the previously used halogens to azodicarbonamide which is iodine free (Pittman, Dailey and Breschi 1969, Blum and Chandra 1970, Sachs and others 1972). By chance the latter substance is weakly goitrogenic but this is not significant in the amounts used (Gafford, Sharry and Pittman 1971). Variation in iodine concentration in this and other foods in different parts of the U.S.A. may account for the large difference in radioactive iodine uptake by the thyroid in euthyroid people throughout that country (Oddie and others 1970).

OTHER METHODS OF IODINE SUPPLEMENTATION

Another method for supplying iodine is the intramuscular injection of iodised oil, which is said to be appropriate for those communities whose public health and medical facilities are not freely available and where endemic goitre is a problem. Communities in central and South America, the Himalayas and New

Guinea have been given this type of prophylaxis with excellent results. The fact that the injection has to be repeated every few years, in communities which are often difficult of access, is the major disadvantage of this method. Many New Guineans and Papuans will not take medication by mouth for reasons of tribal superstition and their nomadism makes regular tablet distribution practically impossible (McCullagh 1963).

IODBASEDOW IN U.S.A.

Unfortunately iodine induced thyrotoxicosis as described by Fyfe, Coindet, Dumas, Rilliet and others has occurred as predicted by Kocher and De Quervain. In 1922 Plummer introduced iodine for the preoperative treatment of thyrotoxicosis (Plummer 1923). Since that time many reports of the abuse of iodine in the treatment of goitre have been published, particularly by Jackson (Jackson 1924). He reported eighteen cases of hyperthyroidism following the excessive use of Lugols iodine, and in 1930 he wrote repeating the warning against the danger of the prolonged use of this solution (Jackson and Ewell 1930).

It seems that the spectacular success of the Akron, Ohio experiment and that in St. Gallen encouraged the use of iodine in larger doses for the treatment of goitre at all ages, particularly in adults. Although the doses were probably not those of Coindet nor those in the first experiment in prophylaxis in France, they were up to 6 mgms potassium iodide daily. Jackson reported that fifty cases with

three deaths had been observed by him and occurred always in people who had long standing nodular goitre. Means and Lerman denied that such a condition existed as they had not seen it in Boston, but later modified their opinion (Means and Lerman 1935). They suggested that in areas of high endemicity as in Switzerland, such a condition might exist but in non-endemic areas it was unlikely. It is interesting that Jackson wrote from an endemic area - Wisconsin, and Means and Lerman from the non-endemic area - Boston. Jackson's views were supported with evidence from Plummer and McClure who noted an increase in the number of goitre operations in Michigan and Minnesota in 1926-27 (Plummer and Boothby 1924, McClure 1934). In 1927 Clute and Mason at the Lahey Clinic reported having seen non-toxic adenomas become toxic after long continued iodine feedings (Clute and Mason 1927). Dinsmore, Boothby and others agreed with Jackson (Dinsmore 1936, Boothby 1935). All were convinced that iodine in therapeutic doses could induce toxicity in some cases of non-toxic nodular goitre but they also agreed that the incidence of the condition was low. Regarding the use of iodine in such cases Coller wrote "iodine after 30 in individuals with adenomatous goitre does not cure and may precipitate hyperthyroidism" (Coller 1926). Goetsch maintained that adolescent goitre was the only type which would respond to iodine (Goetsch 1934). Again it may be remembered that Bruno da Longoburgo and Arnold of Villanova in the 13th century had virtually said the

same thing!

A further disquieting fact reported by Jackson was that if patients ceased taking iodine once thyrotoxicosis was established, a return to the euthyroid state did not necessarily occur. Some patients were toxic two years after ceasing iodine; some patients appeared to become toxic only after long exposure to iodine but others reacted immediately (Jackson and Freeman 1936).

RESPONSE TO DOSE OF IODINE

All of these reports concerned patients with adenomatous goitre who had received large therapeutic doses of iodine, in amounts much higher than the prophylactic dose used by Marine and Kimball or the amount provided by the consumption of iodised salt in Switzerland. Fluck reported a survey carried out by 1600 physicians in 1922-24 (Fluck 1938). They found a thyrotoxicosis incidence of five per hundred thousand population, in areas with or without iodised salt. Their diagnostic criteria are not stated however. Their statement did not contradict that of De Quervain when it is remembered that he spoke of thyrotoxicosis resulting from doses of 0.5 - 1 mgm of iodine daily. The intake in Switzerland in 1922-24 was 100 mcg daily and furthermore, that survey was carried out within a very short time after iodised salt was introduced. For this latter reason, the complete validity of the survey may be questioned. Nevertheless Kimball in 1925 could find only six females out of 2,659 cases of thyrotoxicosis whose disease may have been precipitated by iodine. These were females older than

forty with long standing nodular goitre (Kimball 1925). In 1928 he reported that no toxicity had occurred in 1,299 adults with longstanding goitre after five years consumption of iodised salt (Kimball 1928). On the contrary Eggenberger reported a decrease in the overall incidence of hyperthyroidism after iodised salt (Eggenberger 1938).

The position was well summed up in 1954 by Marine who said "since the dangers of iodbasedow are serious in endemic goitre regions with a high incidence of advanced adenomatous goitre it would seem advisable to use, as Switzerland has, a conservative iodide supplement (1/100,000) rather than greater concentrations." (Marine 1954). This was restated in 1960 by Matovinovic and Ramalingaswami when they said "one thing, however, is clear - namely that large doses (of iodine) should not be administered, for then iodbasedow becomes a real threat." (Matovinovic and Ramalingaswami 1960). On the other hand Matovinovic and Kovacic reported treatment of 1000 adults with large nodular goitre in Yugoslavia, who were given 5-15 mgm potassium iodide per day (Matovinovic, Kovacic and Proserjak 1956). One developed thyroiditis and one iodbasedow -- this incidence will be referred to later. Stanbury reported only one documented case of iodbasedow occurring in Mendoza, Argentina, after daily consumption of 1.5 mgm of potassium iodide for some weeks (Stanbury and others 1954). A similar freedom from toxic reaction to prophylactic iodides in Panama and Guatemala was reported by Scrimshaw and others (Scrimshaw and others 1953) but

Fierro-Benitez reported thyrotoxicosis in three elderly goitrous females in Ecuador (Fierro-Benitez and others 1967). Van Leeuwen described thyrotoxicosis occurring in Holland in 1948 after iodation of bread which produced an average daily consumption of 100 mcg of iodide per person (Van Leeuwen 1954).

CONCLUSIONS

Since iodide has been introduced in the prophylaxis and treatment of goitre, daily doses of 100 mcg (Van Leeuwen) and 500-1500 mcg (De Quervain and Stanbury) have produced some cases of toxicity; doses around 5 mgms daily have produced many cases (Jackson, Plummer and Boothby, McClure, Clute and Mason, Dinsmore); but in some series of longstanding nodular goitre no cases were noted with the consumption of iodised salt (Kimball); even very large doses of iodide in the presence of longstanding nodular goitre have produced a very low level of toxic reactions (Matovinovic and Kovacic). It will be remembered that Richard believed that a daily ingestion of less than 300 mcg of iodine would be without danger of producing thyrotoxicosis.

The use of iodised oil in New Guinea, the Himalayas, and areas of South America has not been followed by any recorded cases of thyrotoxicosis (Buttfield and Hetzel 1969, Ibbertson 1970, Stanbury 1970). It must be said that a small increase in thyrotoxicosis in these communities may not be noticed. Hiding the sick from investigators is well known in backward communities.

Iodide induced goitre, myxoedema and cretinism have been reported since 1945. All of these appear

to occur in patients who have ingested large amounts of iodide over a long period of time and throughout pregnancy in the cases of cretinism. No cases have been reported secondary to goitre prophylaxis with iodised salt or bread. Iodide induced goitre was reported by Laroche and Hirsch in 1960 following a single injection of iodised oil and they discussed the danger of these injections in patients with retrosternal goitre. In susceptible individuals this produced great swelling with respiratory obstruction. They concluded by quoting Janet, who, in 1958 suggested that no iodine should be used in the treatment of endemic goitre and that thyroxine should be used (Laroche and Hirsch 1960). Nevertheless this question remains an open one; certainly the basic fault in the etiology of goitre is iodine deficiency.

"There is indeed no escape from the conclusion that whatever factors, other than simple environmental deficiency of iodine, may be involved at times in the production of goitre, these factors can only exercise their effects through reduction of the available iodine below the level necessary to supply the needs of the thyroid gland. The question as to whether the reduction is brought about directly (by interference with the access of exogenous iodine to the thyroid) or indirectly (by an increase in the demand on the thyroid to produce an iodine-containing secretion) does not affect the argument that it is on iodine that the thyroid specifically depends for the maintenance of its normal structure and function." (Harrington 1933).

CHAPTER 4.

IODINE IN TASMANIA

PLATE 4 - 1

TASMANIA IN RELATION TO THE WORLD



GEOGRAPHY

Physically and politically the island of Tasmania is part of Australia, from the mainland of which, it is separated by the relatively shallow Bass Strait. Physically, it is a part of the East Australian Highlands : politically it is a constituent state of the Commonwealth of Australia. It has an area of 26,215 square miles - almost the same size as Ceylon and a little smaller than Ireland. It's population is about 400,000 divided equally between north and south. The mountains reach just above 5000 feet in height. It lies between 40 and 43½ degrees south of the equator, in the same latitudes as northwestern Spain and northern California north of the equator, and its climate has much in common with these areas (Plate 4 - 1).

Tasmania is a mountainous island and was the seat of extensive glaciation and periglaciation during the last Ice Age, in the Pleistocene era. Periglaciation continues each winter but its average lower limit has ascended from two thousand feet to four thousand feet above sea level. The contour map of Plate 4 - 2 shows the extent of the mountains and Plate 4 - 3 and 4 - 4 show typical glacial valleys and highland lakes. Evidence of glacial and periglacial movement, with consequent washing away of soil, is widespread throughout the island. The valleys are now much wider than the rivers flowing through them, indicating the passage of huge volumes of snow, ice and water, during the Pleistocene era. In the South Island of New Zealand a mountain chain runs from north to south down the west coast and acts as a physical barrier,

PLATE 4 - 2

TASMANIA - CONTOUR MAP

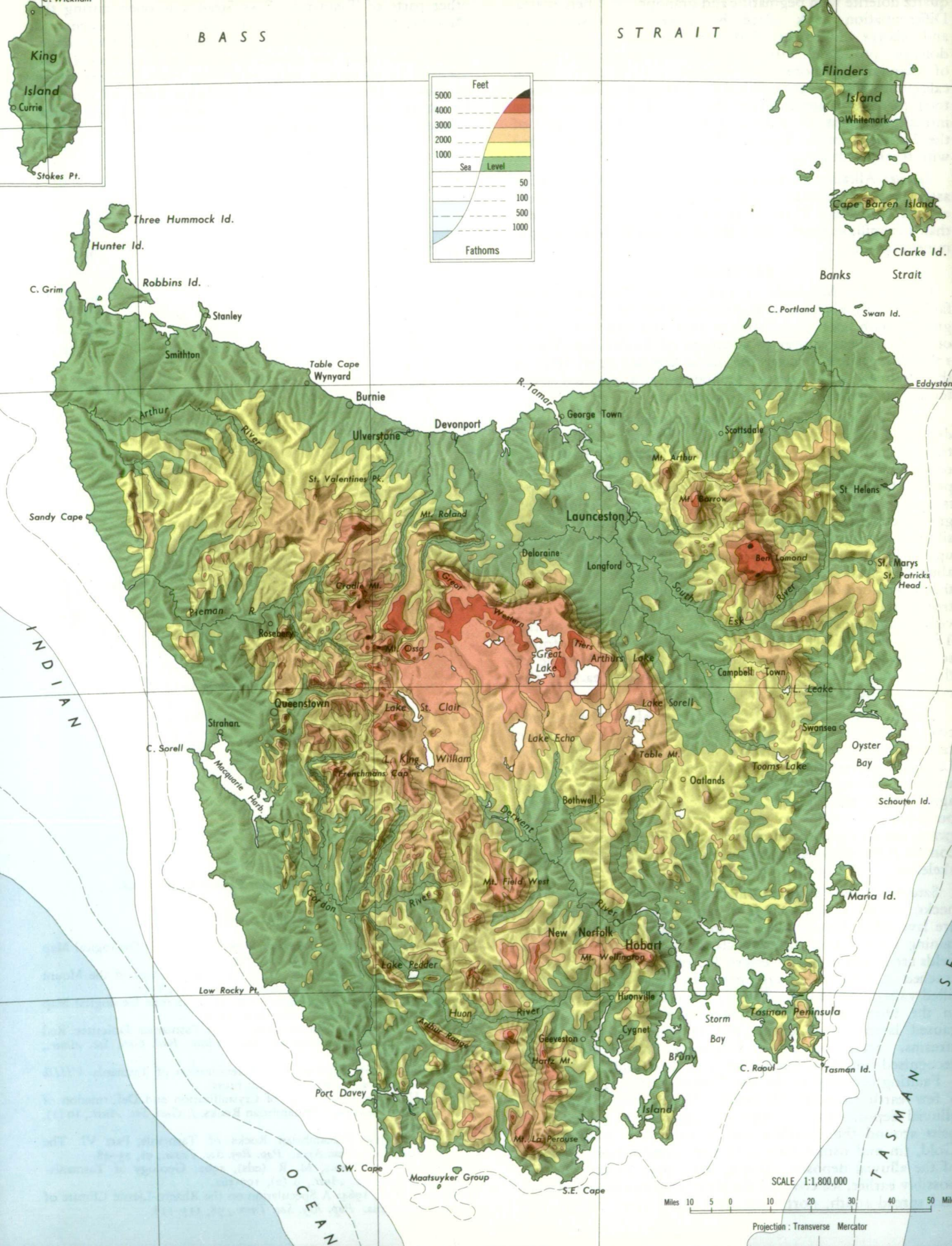


PLATE 4 - 3

THE DENISON RANGE

Even though only a few miles from a motor-road, the Denisons are not yet well known to Tasmanians.

Catching the heaviest snowfalls, the whole range offers magnificent winter scenery. The valley of Rasselas, on the eastern side, could become one of Australia's most favoured resorts for those in search of grand scenery and mountain-walking.

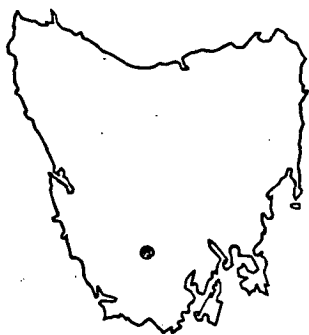
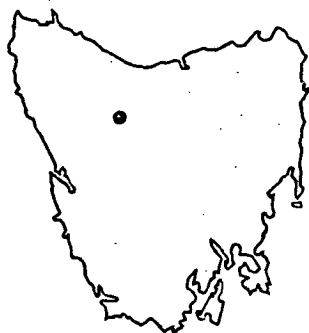


PLATE 4 - 4

CRADLE MOUNTAIN AND DOVE LAKE

At the northern end of Tasmania's best known scenic reserve, Cradle Mt. is easily reached by a good motor-road and is well known to many visitors. Because of this, it has never figured prominently in the author's "wanted" list, but this lovely scene was irresistible.

Walking tracks enable visitors to traverse the shores of Dove Lake, climb Cradle Mt. and Barn Bluff, and, if they are wise and fit, to enjoy the scenic glory of the walk through the Du Cane range to Lake St. Clair.





THE DEMON RANGE



TABLE 4 - 1

IODINE CONCENTRATION IN WATER FROM
SOUTHERN TASMANIA

	IODINE mcg / litre
HOBART TAP WATER	0.6
MT. WELLINGTON NORTH	0.9
MT. WELLINGTON SOUTH	1.3
LAKE CRESCENT	2.8
OYSTER COVE BORE WATER	2.3

TABLE 4 - 2

IODINE CONCENTRATION IN VEGETATION
FROM SOUTHERN TASMANIA

	IODINE mcg / 100 Gm Dry Weight
POA	1.2
WEEDS	6.0
SEDGE	14.0

preventing the replenishment of iodine from the ocean. The prevailing winds in Tasmania as in New Zealand are the Roaring Forties from the west. The map of Tasmania illustrates a similar mountain barrier though not so high on the west coast, extending many miles in depth towards the east. These mountains have large draining river systems, flowing back to both East and West coasts and much of the iodine replenishment, dissolved in rain and snow, passes back to the sea. Thus, rain and snowfall with its dissolved iodine and iodide, fills the highland lakes much of the water flowing back to the sea, leaving the remainder to supply the lowlands where foodstuffs, both animal and vegetable, are grown. The majority of the population live in these lower altitudes.

The soil of Tasmania is poor by world standards and requires repeated fertilisation with superphosphate etc. Different fodder crops have been grown in an attempt to provide adequate and economic production of milk, beef cattle, lamb and wool. The cruciferous plant of the Brassica Class, Chou Moelier, is one which is used extensively and its possible goitrogenic effect will be discussed in a later section, as will the ingestion of cyanates in clover, by sheep and cattle in some parts of the island. It could be assumed from the island's geohistory and geography that iodine deficiency could be present in the environment. This has been confirmed by measurement of the iodine concentration in water from the catchment areas, of the southern part of the State, as shown in Table 4 - 1. The iodine concentration in water of regions where

PLATE 4 - 5

TASMANIA - SOIL TYPES AND DISTRIBUTION

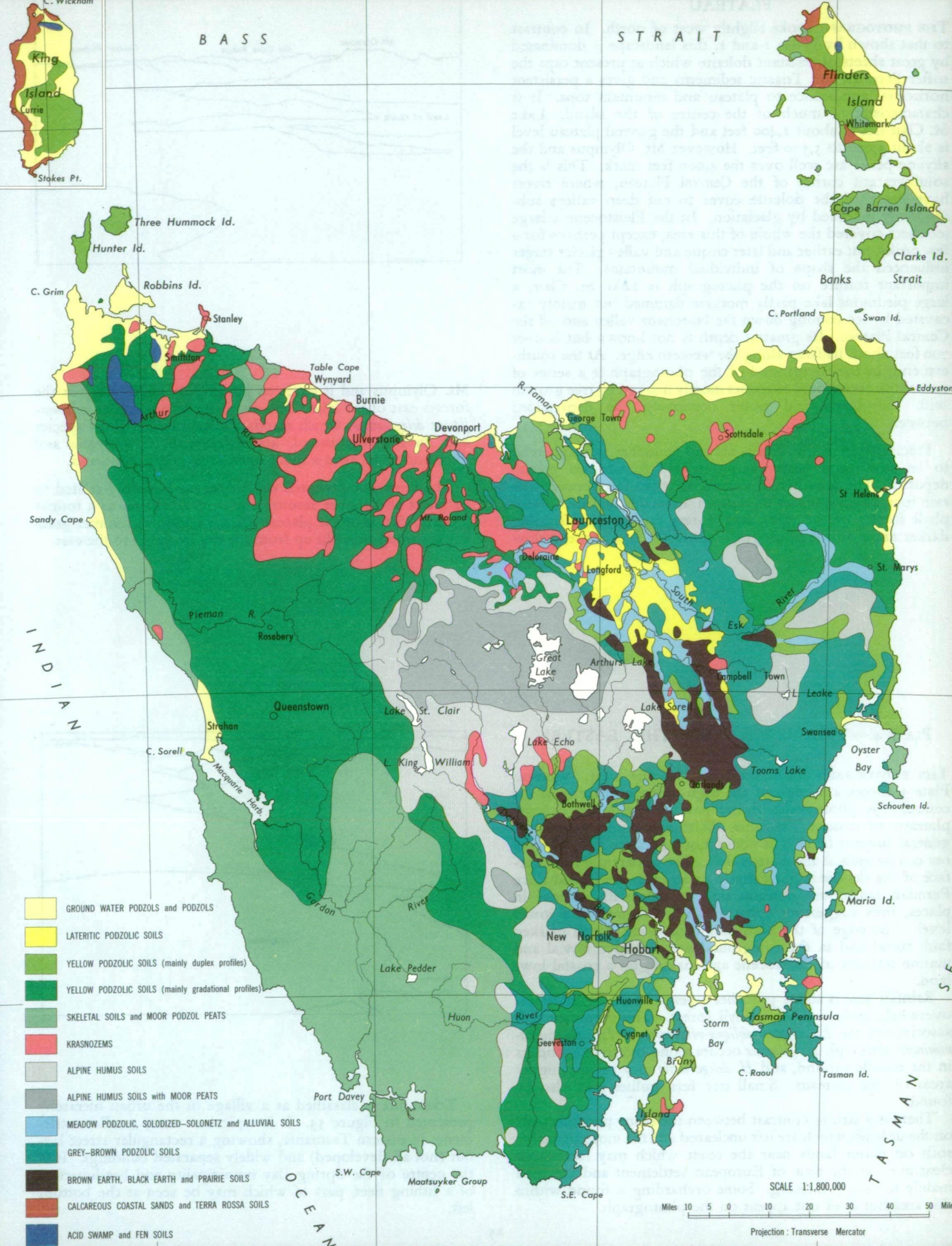


PLATE 4 - 6

TASMANIA - ROCK TYPES AND DISTRIBUTION

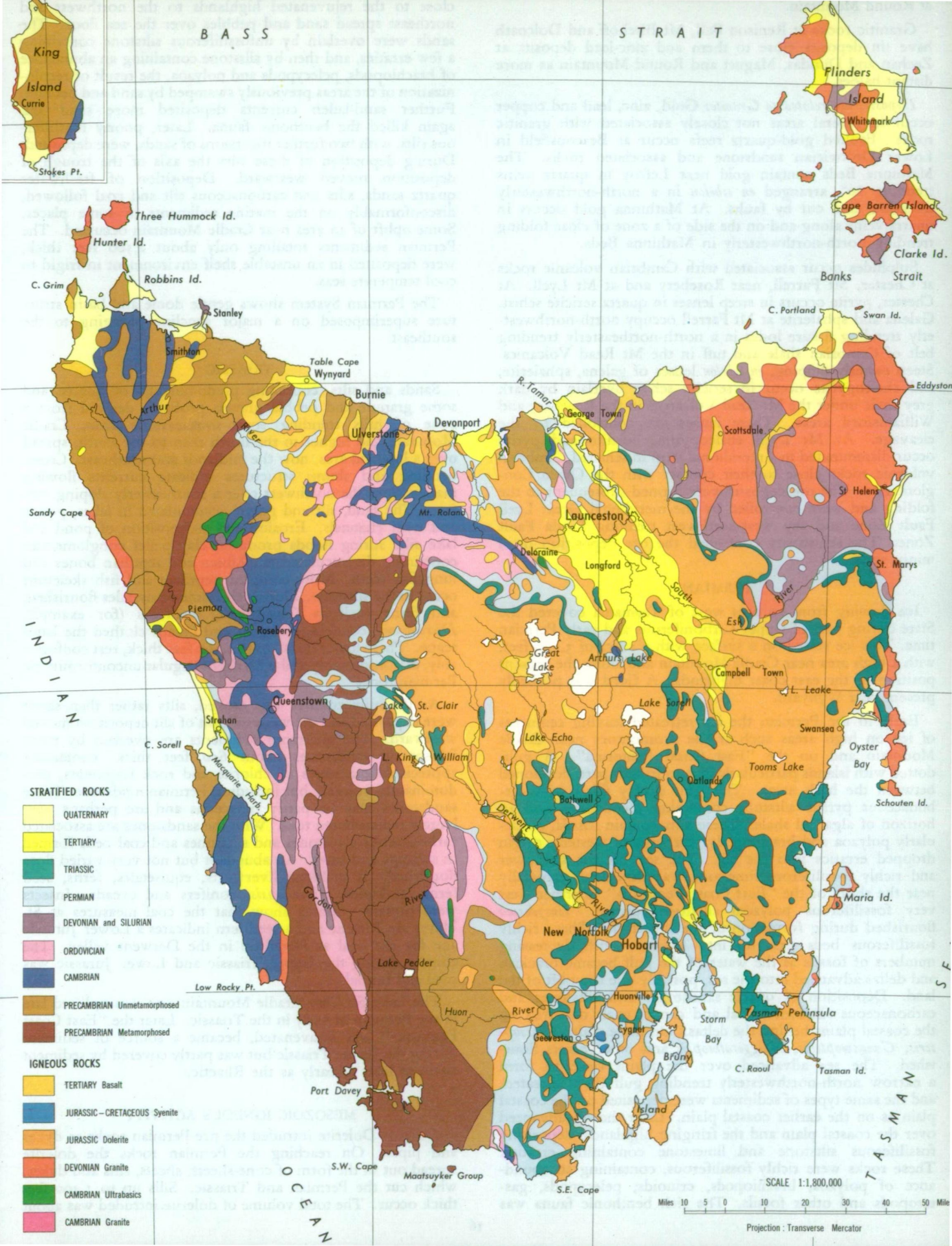
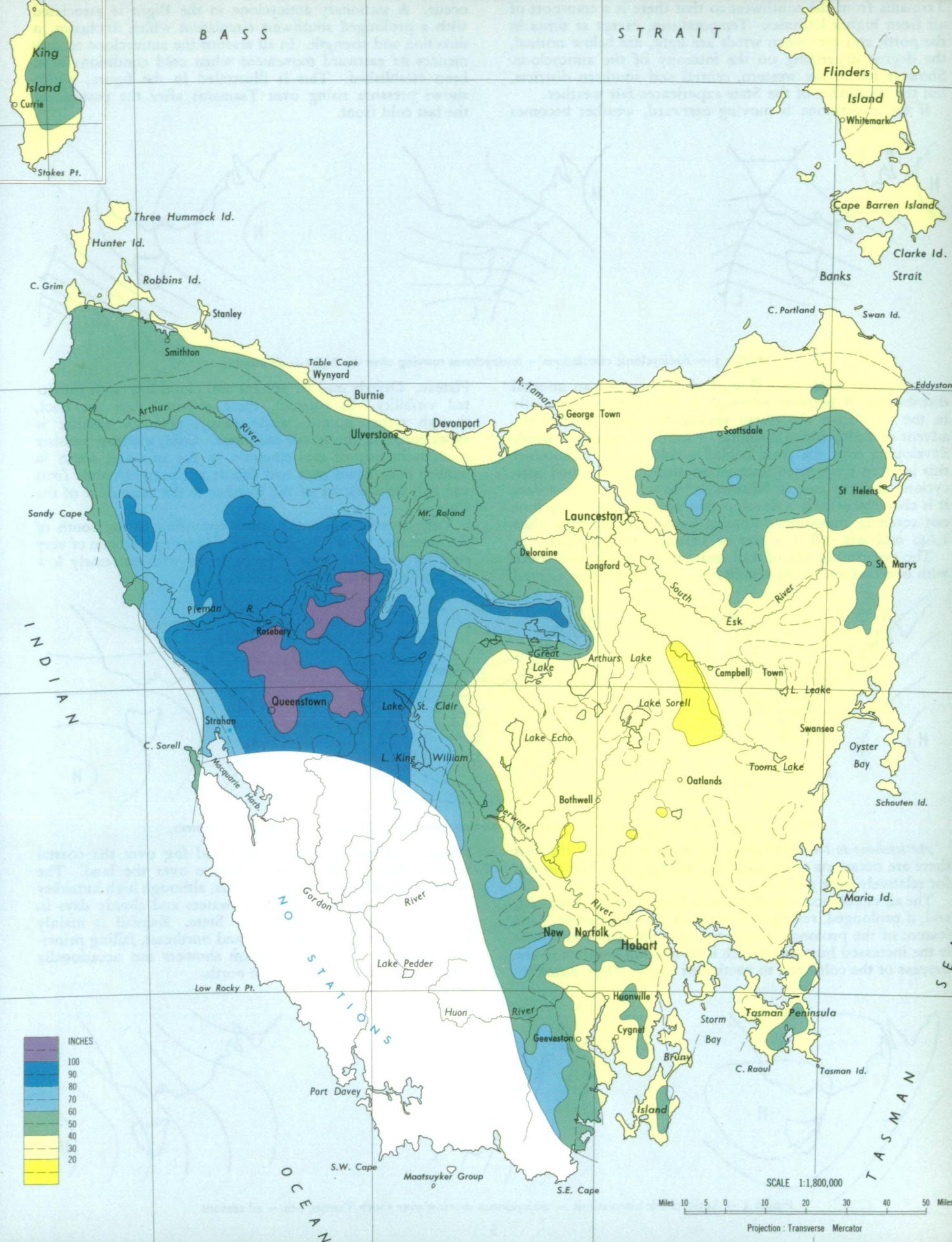


PLATE 4 - 7

TASMANIA - RAINFALL



goitre is not endemic ranges upward from 3 mcg/litre (Murray and others 1948, Koutras and others 1970). Iodine concentration in plants from various areas of Tasmania is seen in Table 4 - 2. Simpson showed that a plant iodine concentration of less than 30 mcg/100 Gm dry weight was associated with goitre in sheep and lambs (Simpson 1930, Butler and others 1956). This is not surprising, when one finds that the ice receded from the lower levels a mere 20,000 years ago. It will be remembered that, for inland areas, Goldschmidt has estimated that hundreds of millenia are required for iodine replacement, because of the very slow cycle from the sea reservoir.

Different soil types are shown in Plate 4 - 5. These consist of peat in the high catchment areas, with abundant humic acid, binding iodine and preventing elution into the rivers. Porous podzols are the principal soils of the lower levels, poor in iodine and not retaining this element when subject to heavy rainfall which takes it below the growth area on the surface. The map shows that these are the two main types of soil in Tasmania.

The geology of the state is shown in Plate 4 - 6. The main rock outcropping is dolerite. Limestone is present in small amounts only and is unlikely to have much effect on the availability of iodine in water.

The annual rainfall, seen in Plate 4 - 7, shows that any weak air movement from the east, coupled with the low rainfall in much of the eastern portion of the state, makes oceanic iodine replenishment from this source, a very protracted process for the eastern half

of the island. The precipitation occurs in these areas onto porous podzols which further lessen the iodine concentration at the surface. Because of its latitude, spring and summer temperatures are not high, thus some of this subterranean water remains, for surface evaporation is not great. Nevertheless, there is some evidence for minor seasonal variation in iodine concentration in herbage (Statham 1971). Goitrous lambs are more likely to be born to ewes grazed on pastures subject to heavy winter rain, suggesting that leaching of iodine into the subsoil may have occurred.

To sum up glaciation, mountainous terrain and the distance from the sea for the main sources of Tasmanian water have combined to produce a state of overall moderate iodine deficiency in the island.

CHAPTER 5

GOITROGENS

THEIR POSSIBLE ROLE IN
PRODUCING ENDEMIC GOITRE
IN TASMANIA

INTRODUCTION

Opinions on the etiology of goitre are many and were discussed in Chapter One. A list of substances thought to be goitrogenic in 1867, is shown in Table 5 - 1.

TABLE 5 - 1

1. WATERS CONTAINING EXCESSIVE QUANTITIES OF :

Suspended matter	Fluoride
Calcium	Barium
Magnesium	Organic matter
Sulphur	Carbonic acid
Gypsum	Volcanic ash
Silica	Coal and metal extractives
2. WATERS DEFICIENT IN :

Oxygen	Phosphate
Iodine	Carbonic acid
Bromine	
3. CONSUMPTION OF :

Vegetables	Fat foods
Milk	Alcohol
Pork	Certain cooking salts
4. CHANGES IN THE ATMOSPHERE :

Humidity	Temperature
Electricity	Sunshine
5. MISCELLANEOUS :

Alcoholism	Consanguinity
Poverty	Unsanitary conditions

THE ETIOLOGY OF GOITRE GIVEN
BY SAINT LAGER IN 1867.

Possible causes of goitre in 1937, are shown in Table 5 - 2.

TABLE 5 - 2

1. Faulty diet:
 - A. Excess of : fat, fatty acids, and lime
 - B. Deficiency of : iodine, vitamins A and C, protein, phosphate.
 - C. Goiter-producing substances -- cyanogen compounds.
 - D. Lack of antigoitrogens present in green grass, alfalfa, steamed cabbage juice, sprouted legumes, and carrots.
2. Chemical substances:
Calcium, boron, silica, tellurium, organic acids, amines, cyanides, coal tar.
3. Unsanitary conditions.
4. Infections.

THE ETIOLOGY OF GOITRE GIVEN
BY McCARRISON IN 1937.

Stanbury and Querido (1956) could find no correlation between goitre formation, fat intake, malnutrition or vitamin deficiency. Roche and Lissitzky (1960) could find no causative relationship between protein deficiency, excess of fat and carbohydrate and endemic goitre. Astwood (1949) suggested that in cold climates, during active growth, good nutrition allowed some physiological enlargement of the thyroid and a failure of such enlargement may be evidence of dietary deficiency. One presumes that if iodine were the sole deficiency, the "physiological" enlargement would be increased. This is pure speculation of course. Over the years many foods have been suspected

of being goitrogenic, e.g. soya beans, peanuts, radishes, carrots and pears. No goitrogenic activity has been found in any of these foods, but they have been suspected in iodine deficient areas of the world. It seems fairly certain that iodine deficiency is the goitrogenic factor in these cases. It is important to realise that the results of animal experiments cannot be directly applied to man, particularly concerning goitrogens. For example, the relative potency of goitrin to propyl thiouracil is 1:50 in the rat, but 1.33 : 1 in man. Some sulphonamides are goitrogenic in animals but not in man. Excluding these unlikely causes of goitre given above the subject will be discussed in the following order :

1. Probable food goitrogens:
 - (a) in Brassica plants
 - (b) in milk
 - (c) in other foods
2. Inorganic chemical substances
3. Unsanitary conditions
4. Infection
5. Methyl xanthines
6. Antigoitrogens.

1. PROBABLE FOOD GOITROGENS

(a) BRASSICA PLANTS

Following the report of "cabbage goitre" by Chesney, Clawson and Webster (1928) much investigation into plant goitrogens has been carried out. Active plant goitrogens can be divided into the following classes:

- (i) Inorganic Thiocyanates
- (ii) Thioglycosides
- (iii) Organic Thiocyanates

(i) Inorganic Thiocyanates

These substances are present in a great variety of plants. In combination with low iodine intake they may produce goitre in animals and man, but it is doubtful if a sufficient amount to cause goitre is consumed by man. Animals, particularly sheep, feeding on thiocyanate rich clovers develop goitre if there is a low iodine concentration in the pasture. The ability of plants to absorb iodine from the soil varies. Butler and others have shown that the iodine content of some clovers is inversely proportional to their cyanate concentration. Thus, some clovers are very goitrogenic when iodine is low and cyanate is high, whilst others are weakly goitrogenic (Butler and others 1956).

Although Chesney and Marine were able to produce "Cabbage goitre" in rabbits many other workers were unable to do so (Chesney, Clawson and Webster 1928, Marine, Baumann and Cipra 1929). It now seems clear that to produce goitre in rabbits iodine deficiency as well as a goitrogen is necessary, unless thiocyanate or its nitrile precursor are ingested in very large amounts. Even then goitre was not produced in every animal. The same occurred in humans as a side effect in the treatment of hypertension with thiocyanate (Barker 1936):; but only three of 45 patients, receiving the huge daily dose of 300 mgm

of potassium thiocyanate, developed goitre. Their blood cyanate level varied between 5 and 7 mgm per 100 ml.

(ii) Thioglycosides

In New Zealand, it was found that goitre in rabbits was produced more frequently if the animals were fed on brassica plants other than cabbage, particularly if the root system or seeds were eaten (Hercus and Aitken 1933). Some seeds, notably rape, were highly goitrogenic only if unheated, whereas others, notably mustard plants were unaffected by heat (Hercus and Purves 1936). Further work, by the New Zealand group, demonstrated that previous hypophysectomy prevented the development of rape seed goitre (Kennedy and Purves 1941, Griesbach, Kennedy and Purves 1941). They also found that iodine gave partial protection against rape seed goitre, but full protection for the animal required thyroxine.

Thus a distinction was made between two groups of goitrogen:

1. a heat stable, thiocyanate active in iodine deficiency and overcome by excess iodine
2. a heat labile goitrogen requiring thyroxine for adequate protection of the animal.

Because the response of different animal species varied, the goitrogenic properties of the plants were tested in human volunteers. Foods, which interfered with radioiodine uptake, were fractionated by Astwood and his coworkers. They chose the yellow turnip because of its ability to depress radioiodine uptake in both animals and man (Astwood 1949). Purifi-

cation of an aqueous extract yielded the thioglycoside L-5-vinyl-2-thiooxazolidone, to which the name goitrin was given. Further, work showed that a precursor, progoitrin, was acted upon by a substance present in the plant called myrosin, converting it to goitrin (Greer 1956). Myrosin was found, on later examination, to be the heat labile substance, observed by the New Zealanders. This substance is necessary to produce goitre in the rabbit, but in humans bacteria of the intestine are able to convert progoitrin to goitrin. Hence in man, both groups are capable of a goitrogenic effect even after heating. Goitrin has an effect equal to thiouracil and was found to be more abundant in the seeds of turnip, cabbage, rape, kale and other brassicae (Greer 1964). It was not detected in the edible portions of cabbage, kale, broccoli or cauliflower.

(iii) Organic Thiocyanates

The third group of goitrogenic compounds found in the brassica group of plants are isothiocyanates (Astwood 1949). Their effect in animals was described by Bachelard and Trikojus. In non ruminants the material acts as a thiocyanate but in ruminants one of this group, cheirolin is converted after three hours in the rumen, to dicheirolin thiourea. This substance has the opposite effect to that expected. Whereas thiourea and thiocyanate are both goitrogenic, a combination of them is much less active, if at all (Bachelard and Trikojus 1964).

(b) MILK

Clements reported a survey for goitre in Tasmanian

TABLE 5 - 3

TASMANIAN PASTURE CONTAMINANTS

NAMES	COMMON NAME	GLYCOSIDES	
		MAJOR	MINOR
BRASSICA CAMPESTUS	TURNIP	1	4
SISYMBRIUM OFFICIANALE	MUSTARD	1	3
SISYMBRIUM ORIENTALE	MUSTARD	1	1
RAPHANUS RAPHANISTRUM	RADISH	2	2
SINAPIS AVERSE	CHARLOCK	1	1

schoolchildren in 1949, and recommended prophylaxis in the form of a weekly dose of 10 mgm. of potassium iodide. Surveys, in the succeeding years, showed some fall in goitre prevalence but the result was a little disappointing (Clements 1954). Perhaps the tablets were not being distributed properly in some areas but other reasons for the failure were sought. During this period, a scheme to provide one third of a pint of milk daily to all schoolchildren, was introduced by the Government. It required an increase in milk production, particularly in the winter and a search was made for new winter pasture plants. The plant *brassica oleracea*, var. *acephalata* (choumoellier or marrow-stem kale) was chosen and by the mid 1950's, was widespread throughout the island. It was noted also that weeds, contaminating pastures at other times of the year, contained thioglycosides and these are given in Table 5 - 3 (Bachelard and Trikojus 1964).

Clements and Wishart suggested that goitrogens from the brassicae were eaten by cows, secreted into milk and drunk by the children (Clements and Wishart 1956). Their first experiments agreed with similar ones performed by Greer and Astwood, in that milk seemed to interfere with radioiodine uptake in human volunteers (Greer and Astwood 1948). Neither group was able to show this effect in subsequent experiments. In the light of Astwood's original work, it is unlikely that much progoitrin or goitrin would have been eaten by the cows. He showed that the brassicae store these substances in the root system and seeds with very

little in the foliage.

There seems no doubt, that a substance present in kale is goitrogenic in the rabbit but Greene, Farran and Glascock could find no difference in thyroid size in humans consuming milk, produced from pastures with and without kale (Greene, Farran and Glascock 1958). They conclude, "it seems therefore that some explanation should be sought other than the presence of a specific goitrogenic substance in kale milk." Arstila, Krusius and Peltola showed that six out of nine milk specimens from a goitrous region, contained goitrin in concentrations of 35-100 mcg / litre but the daily consumption of 3-4 pints of such milk, for five weeks, was necessary to depress radio-iodine uptake in humans (Arstila, Krusius and Peltola 1969). If cruciferous weeds in the pastures were destroyed, goitrin disappeared from milk. Virtanen and others in 1959 found only 0.05 per cent of goitrin fed to cows was recovered in milk, no matter if fed as choumoellier, green rape or crystalline goitrin. When progoitrin was used, the yield of goitrin in milk was practically nil. Cows fed on cruciferous weeds, had less than 100 mcg goitrin per litre of milk, which is insufficient to affect thyroid function when consumed by man (Virtanen 1963).

The isothiocyanate group of brassica goitrogens, as typified by cheirolin, has been shown to be inactivated in the rumen and in any case this substance is not found in Tasmanian pastures (Bachelard and Trikojus 1964).

The possibility that a goitrogen in milk was of

inorganic thiocyanate origin received some support from work done in New Zealand, by Wright. He showed that milk, from cows fed on pastures with high thiocyanate content, produced a small discharge of radioiodine in volunteers who drank it (Wright 1958), but once again this work could not be reproduced. Allcroft and Salt reported an increase in thiocyanate in pasture at the time of most rapid growth, which, in the presence of iodine deficiency, was associated with goitre in animals. It could be prevented by the addition of potassium iodate 24 lbs per acre. This fertiliser also produced an increase in milk iodine from cows grazing on the pasture, demonstrating the uptake of the iodate by the plants (Allcroft 1961). Of course, relative iodine deficiency was the probable cause in this case and the thiocyanate played a minor role, if any.

During the period of most rapid growth, rainfall is at its highest in Tasmania. Work done at the University of Tasmania suggests, that not only is iodine carried into the subsoil at this time, but it is also leached from the pasture plants (Statham 1971). Virtanen and Gmelin reported data indicating that effective increases in thiocyanate in milk is unlikely. They fed 6 grams of thiocyanate daily to cows, without producing much increase in concentration in milk (Virtanen 1959, 1961, 1963). In summary, it must be said that in spite of repetition in the literature, there is no evidence for any goitrogenic activity in milk in Tasmania, either thiocyanate or thioglycoside. Reports of the goitrogenic effects

of milk continue from some parts of the world (Munoz-Rodriguez 1970).

(c) OTHER FOODS

The effects of food shortage on the continent of Europe and the island of Formosa during the Second World War were reported by Meulengracht, Iversen, Bastenie and Chen. They reported an increased prevalence of goitre. Many areas of Europe and Formosa are iodine deficient or marginally so. The addition of goitrogens to the diet would increase the tendency of people living in these areas to develop goitre. During the war there was an increased consumption of cabbage, kale and turnip by these populations leading to the increased incidence of goitre. Both heat stable and labile goitrogens are present in these foods (Meulengracht 1945, Iversen 1948, Bastenie 1947, Chen 1954). As cabbage leaves contain thiocyanate only, large amounts of this vegetable would have to be eaten. Langer has shown that depression of radioiodine uptake requires the intake of 0.5 Kg. of cabbage daily for fourteen days (Langer 1964). Recently this worker reported a small variation in blood thiocyanate levels throughout the year, to account for the seasonal variation in goitre prevalence noted in Czechoslovakia, as in other parts of the world (Langer 1964). But the range is very small and concentrations do not exceed the normal value of 0.2 - 0.5 mgm. per 100 ml. much less than that maintained by Barker, in the treatment of hypertension.

Hales and others, believe that seasonal variation of goitre prevalence in N.S.W. Australia, is due to

variation in water iodine concentration, with lowering of the concentration of the element, by melting snow in the spring, diluting the water supply which comes from lower altitudes with more natural iodine, as described in Chapters 3 and 4 (Hales 1969). In Tasmania, the suggestion of Gibson, Howeler and Clements that a goitrogen was the cause of seasonal variation was questioned (Connolly 1971, Gibson, Howeler and Clements 1960). I suggested that there was a natural seasonal variation in thyroid function, possibly mediated through thyroid releasing factor and thyroid stimulating hormone, responding to the change in hours of daylight. Support for this hypothesis comes from work in animals by Henneman, Kilpatrick, Wilson and Randall (Henneman 1964, Kilpatrick 1964, Randall 1970). Sensitivity to T.S.H. has been shown by Bray to be increased by previous iodine depletion in rats (Bray 1968). However, Burke has shown that iodide repletion depresses the output of T.S.H. directly and therefore its goitrogenic activity in sheep (Burke 1970). The Tasmanian experience of Gibson and others, precludes the presence of iodine deficiency, as the children were receiving large doses (10-20 mgm potassium iodide weekly), not enough though, to produce the iodide goitre described by Wolff and others (Wolff 1969). A seasonal variation in thyroid function, grafted onto preexisting goitre from iodine deficiency, seems to best fit the situation in Tasmania, where no goitrogenic activity in humans has been demonstrated in spite of extensive investigation. The clear seasonal variation in the incidence of thyro-

toxicosis reported from Denmark by Iversen in 1948 is seen also in Tasmania (Iversen 1948, Connolly 1971). The increased incidence of thyrotoxicosis in Tasmania in Spring and Summer immediately following the rapid growth period of plants containing possible goitrogenic substances, makes the latter an unlikely factor in the production of goitre. Substances which produce goitre by blocking iodine metabolism should produce a fall rather than a rise in the incidence of thyrotoxicosis.

Greer and Milne suggested that sulphonamide goitrogens described originally by MacKenzie, may be operating in Tasmania (Greer and Milne 1962, MacKenzie 1942). Iodide increases the goitrogenic effect of this group in animals in contrast to decrease with thiocyanate and little effect with goitrin types. This may have explained the apparent increase in goitre prevalence in the children, in spite of extra iodine. But it has been shown that sulphonamides have little if any, goitrogenic effect in humans, and recent surveys of children in Tasmania, since iodation of bread, show almost complete disappearance of goitre (Clements, Gibson and Howeler-Coy 1970).

Little evidence remains to support the theory of a food goitrogen, of any significance, operating in Tasmania, although it cannot be denied that a minimal effect by one or more goitrogens, in the presence of previous iodine deficiency, may have been present.

2. INORGANIC CHEMICAL SUBSTANCES

Calcium, magnesium, fluorine and phosphate are found together frequently in nature. Steyn found that large doses of calcium and fluorine were goitrogenic in experimental animals and suggested that goitre in the Northwest Province of South Africa was due to excess of these elements, rather than iodine deficiency (Steyn 1949). Hodge and Smith, however, have reviewed the effects of fluoride on the structure and function of the thyroid in man and experimental animals. They concluded that there was no significant effect, except at such high levels, which would produce other obvious deleterious reactions (Hodge 1965). Pastan in 1968, showed that fluoride increased cyclic A.M.P. activity and glucose ^{14}C oxidation in thyroid cells, as does T.S.H. but unlike the latter, fluoride failed to induce the formation of intracellular colloid droplets. Thus, only some of the parameters of thyroid cell hyperplasia can be demonstrated and the dose required to produce them may cause the reactions mentioned by Hodge and Smith (Pastan 1968). On the other hand Stanbury, reviewing the conclusions of the W.H.O. Conference on endemic goitre in 1952, suggested that there was enough evidence from older literature to reinvestigate the relationship between hardness of water, calcium intake and endemic goitre (Stanbury 1952). Day and Powell-Jackson suggest a direct relationship between fluorine concentration in drinking water and goitre prevalence in Himalayan villages which are also iodine deficient. A similar effect was noted with increasing hardness of the water

in these areas (Day and Powell-Jackson 1972).

The mineral concentrations in Tasmania have been discussed in a previous chapter, where it was shown that excess calcium, magnesium and phosphate does not occur. Tasmanian water is soft and far from having excess fluoride, the state as a whole is deficient in this element. Concentrations of this element have been determined in water throughout Tasmania. No concentration greater than 0.05 parts per million was found; indeed the island would have one of the lowest fluoride concentration in water in the world (Crisp 1968). Recently fluoride has been added to some water supplied as prophylaxis against dental caries, but universal fluoridation is not complete at this time. The other substances mentioned by McCarrison have not been found to any extent in Tasmania. Cobalt has been shown by Kriss and others to block the uptake of iodide and decrease organic binding of the ion by the thyroid. Pharmacologic doses in the treatment of anaemia are required to produce goitre and there has been no report of the syndrome occurring from this trace element found naturally (Kriss 1956).

3. UNSANITARY CONDITIONS

Like McCarrison who associated goitre with the unsanitary state of some of the Indian villages, Khavin and Nikolayev contrasted the goitre rate in the improved section of Samarkand with the old unsanitary section of the city. They found much greater prevalence of goitre in the latter (Khavin undated). It is difficult to be sure which of many factors involved in public health improvement may have caused

TABLE 5 - 4

BOTHWELL AREA DRINKING WATER - FEBRUARY 1970

AREA	FAECAL COLI / 100 ml	IODINE ug/litre
LAKE CRESCENT	14	2.8
NORWOOD-DENNISTOUN BOUNDARY	800	3.1
NANT BRIDGE	1000	3.9
THORPE	1400	3.7
PUMP INTAKE	1200	3.9
TOWN RESERVOIR	30	3.9
TOWN RETICULATION	0	3.9

the decrease. No such difference in prevalence has been found in Tasmania where our surveys have shown goitre prevalence to be the same in all social groups.

Hettche reported the goitrogenic effects of urochromes in drinking water from shallow wells in Germany (Hettche 1956). I considered this possibility for Tasmania, as large areas have been used for grazing sheep and cattle, with possible contamination of the water. The best index for this is the growth of animal coliform organisms. The water of various areas in Tasmania is checked regularly, samples being incubated at 44⁰ C. on media favouring the growth of these bacteria. No faecal contamination of water from the highlands has been found at any time. This water supplies the Derwent Valley and Greater Hobart, where three quarters of the population of Southern Tasmania live. Contamination of the lower Derwent River is high occasionally, but this water is not suitable for drinking. One area in the midlands of Southern Tasmania has a basic supply which is heavily contaminated at times. Table 5 - 4 shows the increasing concentration of contaminants as the water flows from the catchment area at Lake Crescent to Bothwell, the central town of the area.

The water is chlorinated but no filtration is carried out resulting in urochromes and other organic material passing into the town reticulation. The river, above the reservoirs, is used for irrigation, particularly in the summer months, which causes the contamination. The water carries the organic material and organisms from the soil back to the river and

TABLE 5 - 5

INCREASING IODINE CONCENTRATION IN
WATER LAKE CRESCENT TO BOTHWELL
NOVEMBER 1971

SAMPLING AREA	Ug / litre
LAKE CRESCENT	2.9
BLACK SNAKE BRIDGE	3.2
DENNISTOUN INTAKE	4.2
DENNISTOUN / NORWOOD	5.2
NANT BRIDGE	5.5
THORPE	7.2
BOTHWELL	8.0

thence to the reservoir. Nevertheless iodine deficiency is present also. Lake Crescent has an iodine concentration of only 2.8 micrograms / litre, and Statham has shown that the pastures are low in iodine in areas where sheep and lamb goitre is common (Statham 1971). One has to realise that irrigation not only causes contamination with coliforms from the soil, but sometimes adds iodine to the river. This comes from iodine present in the soil naturally, but also from sheep urine. The animals are given a drench, containing iodide at least once and sometimes twice per year. The combined effect of iodide drenching and irrigation on the concentration of iodine in the river is shown in Table 5 - 5. Filtration of the water to remove organic solids made no difference to the iodine estimation showing it was in solution.

The pastures which produce goitre grow on porous soil, where iodine is carried by the rain into the subsoil, away from the growing vegetation. Lamb goitre is much less common when ewes graze on heavy soil pastures which will not allow the iodine to pass below the vegetation. A similar situation of water contamination applies in small areas in the Huon Valley, south of Hobart, where river water is used for irrigation and drinking. This area serves a small population and the water is as iodine deficient as at Bothwell. Indeed the water comes from the slopes of Mt. Wellington which has been shown in Chapter 4 to be very iodine deficient (1.3 mcg / litre). The combined populations exposed to the

possible goitrogenic effect of urochrome when irrigation is occurring during the summer, is less than 5 per cent of the total for Southern Tasmania, more than 95 per cent receiving a pure water supply (Tasmanian Year Book 1971). Further, no other workers have been able to demonstrate that urochrome is an active goitrogen.

The studies of Gaetan and others in the Cauca Valley of Colombia in South America, revealed high endemicity of goitre in the presence of high urinary iodine excretion (220 mcg. daily and higher). They found substances in drinking water, containing sulphur with a molecular weight of 250 approximately, which are volatile and appear to cause goitre in rats. The compound or compounds have not been identified yet but may represent a new class of goitrogen (Gaetan 1968, Wahner 1971).

4. INFECTION

McCarrison and Greenwald, working separately, believe that infection by an unknown organism is the primary cause of goitre. (McCarrison 1906, McCarrison 1908, McCarrison 1927). Greenwald has reviewed the incidence of thyrotoxicosis, with preceding goitre, in many countries and claims that most cases, recorded in world literature, could have begun with an infection contracted between 1919 and 1923 (Greenwald 1968, Greenwald 1969). Meulengracht in 1949, stated "the disease might be entirely or in part caused by a specific infectious agent of unknown nature." He was writing of thyrotoxicosis but the inference of

preceding goitre remains, as with the opinion of Greenwald (Meulengracht 1949).

McCarrison thought that water pollution with infection caused goitre in the Chitral and Gilgit Fan areas of northern India. The percentage of goitre in a village upstream was 11.8 and 45.6 downstream. In a boarding school, whose water supply was polluted, goitre prevalence was 66 per cent. When the water supply only was changed, there was a marked reduction in prevalence. Boiling the water in these areas prevented goitre in human volunteers but was goitrogenic otherwise. Unfortunately this work cannot be reproduced. McCarrison's eventual belief was that goitre was due to focal infection, a popular theory for the cause of many other diseases at this time. Pern, in Australia, was treating goitrous people by excision of various areas of "focal sepsis" and it is interesting to read McCarrison's letter to him in 1931 - "I am glad you have stuck out against the generally accepted opinion that goitre was due to lack of iodine and I am interested to hear of your successful cures of the condition by the removal of the focal infections. I am quite sure that where men have failed to cure goitres, they have overlooked some focus of infection somewhere." (Pern 1931).

An association between focal sepsis and thyroid enlargement, or indeed, any other condition, has never been supported statistically. No one has ever attacked the problem of goitre in Tasmania by removing "focal sepsis" but no evidence for its presence has been produced.

5. METHYLYXANTHINES

These substances have been described recently by Wolff and Varonne. They appear to increase thyroid weight without any increase in thyrotrophin, suggesting that they make the gland more sensitive to T.S.H. similar to that of iodine deficiency as suggested by Bray (Wolff 1969, Bray 1968). It will be shown in a later chapter that a marginal effect at most, has been experienced in Tasmania.

6. ANTIGOITROGENS

McCarrison thought that these substances existed in the foods given in his list, but it seems fairly certain now that the substances were only antigoitrogenic if they were grown in areas, where iodine was in normal soil concentration and thus supplied iodine to people with iodine deficiency goitre. The only antigoitrogens, so far found in practice throughout the world, are thyroid hormones and iodine.

SUMMARY.

It would appear that iodine deficiency remains the cause of goitre in Tasmania. There is no evidence for any of the goitrogenic factors discussed above, acting to any marked extent. No parallel to the experience of Delange and others on the island of Idjwi, and Gaetan in Colombia, can be found. Iodine deficiency throughout the island of Idjwi was reported, but the incidence of goitre in the north was 54.4 per cent and in the southwest only 5.3 per cent. They suggested that a goitrogen may be

operating marginally in the northern area (Delange 1968). A further recent report from Delange suggests that a more effective response to increased T.S.H. on the island of Idjwi, Democratic Republic of the Congo, may explain the different goitre prevalence in the two areas of the island. He can give no reason for the different responses, however. No goitrogens have been isolated from food or water by these workers (Delange 1971).

Equally, the idea of McGirr, Greig and others, that some people have an inherited ability to deal with iodine deficient states more efficiently, without the production of a goitre, might apply (McGirr 1968). Some support for this comes from recent work where a statistically significant increase in the percentage of people showing immunoglobulin M occurs in patients with goitre in the New York area (Werner 1970). This suggests some difference in individual inheritance, with consequent difference in reaction to changes in the environment. If there is a genetic contribution it is probably minor, being far outweighed by other factors, the principal one being iodine deficiency (Stanbury 1970).

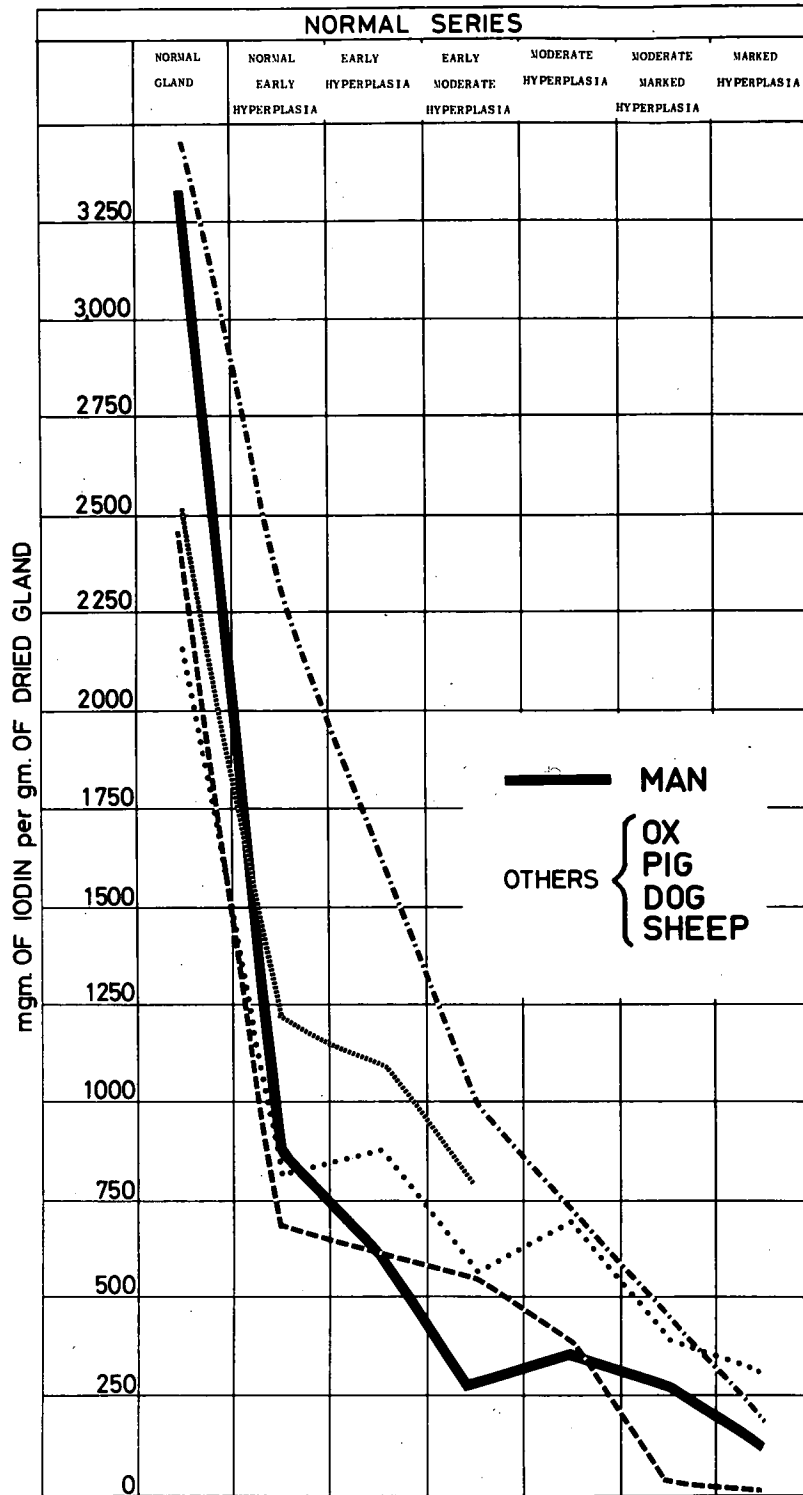
CHAPTER 6

PATHOLOGY OF GOITRE IN TASMANIA

FIGURE 6 - 1

THE INVERSE RELATIONSHIP OF
THYROID IODINE CONCENTRATION
AND HYPERPLASIA OF THE GLAND

FIG 6-1



CURVES COMPILED FROM THE AVERAGE IODIN CONTENTS PER GRAM OF DRIED GLAND OF THE NORMAL SERIES OF HYPERPLASIAS.

(MARINE & LENHART 1909)

INTRODUCTION

In 1909 Marine and Williams showed that the degree of hyperplasia of thyroid cells decreased in direct proportion to the concentration of iodine in the thyroid gland. This is shown in Figure 6 - 1 which is reproduced from the original article. The low concentration of iodine in plants, soil and water from Tasmania has been discussed in previous chapters, but the intake of iodine by man has been increased from several sources and these will be described later. To obtain some idea of the effect of low available iodine in nature in Tasmania, without additions to the environment, animal studies were undertaken. Pregnant ewes grazing on iodine deficient pastures produced many stillborn lambs and those dying in the early neonatal period. Some of these ewes were given intramuscular iodised oil and surviving goitrous lambs were given extra iodine. The different patterns of thyroid histology resulting in these groups were studied and representative sections are presented in this chapter. It is not suggested that goitre in the human was as active. Extra iodine from other sources has been available for many years but not in sufficient quantity to prevent the development of this condition. Thyroid pathology of all types occurs in the state and examples are shown in the succeeding plates.

GOITRE STUDIES IN SHEEP

The effect of natural iodine deficiency before extra iodine was added, can be seen in the thyroid glands of lambs and sheep in Tasmania. These animals were chosen because they were readily available, they

PLATE 6 - 1

LAMB GOITRE FOLLOWING IODINE DEFICIENCY
IN THE PREGNANT EWE.

MARKED HYPERPLASIA OF THYROID CELLS.
COLLOID IS ABSORBED AND POOR STAINING
IS SHOWN.

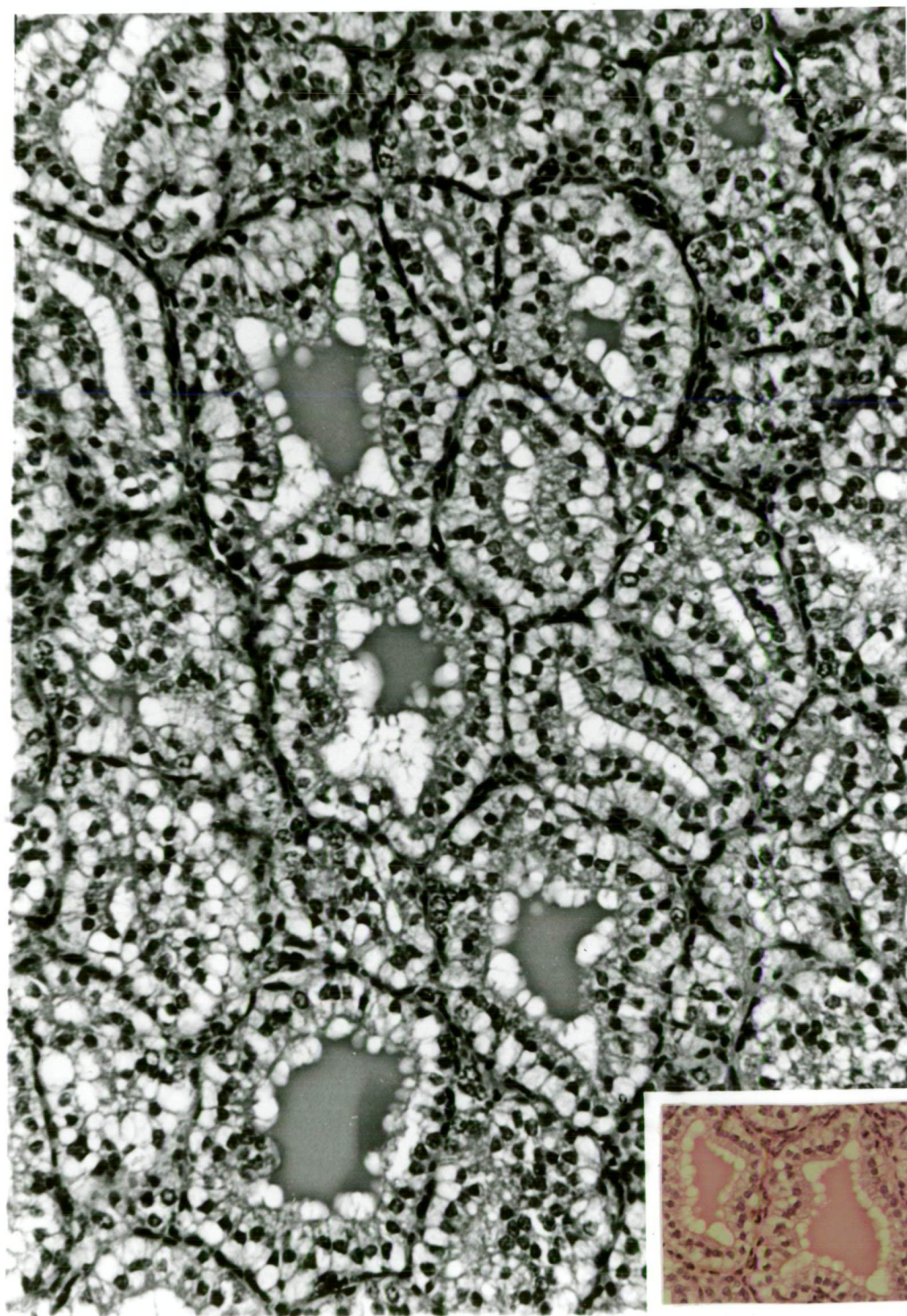


PLATE 6 - 2

LAMB GOITRE FOLLOWING IODINE DEFICIENCY
IN THE PREGNANT EWE

HYPERPLASIA OF THYROID CELLS IS LESS
MARKED THAN SHOWN IN PLATE 6 - 1.

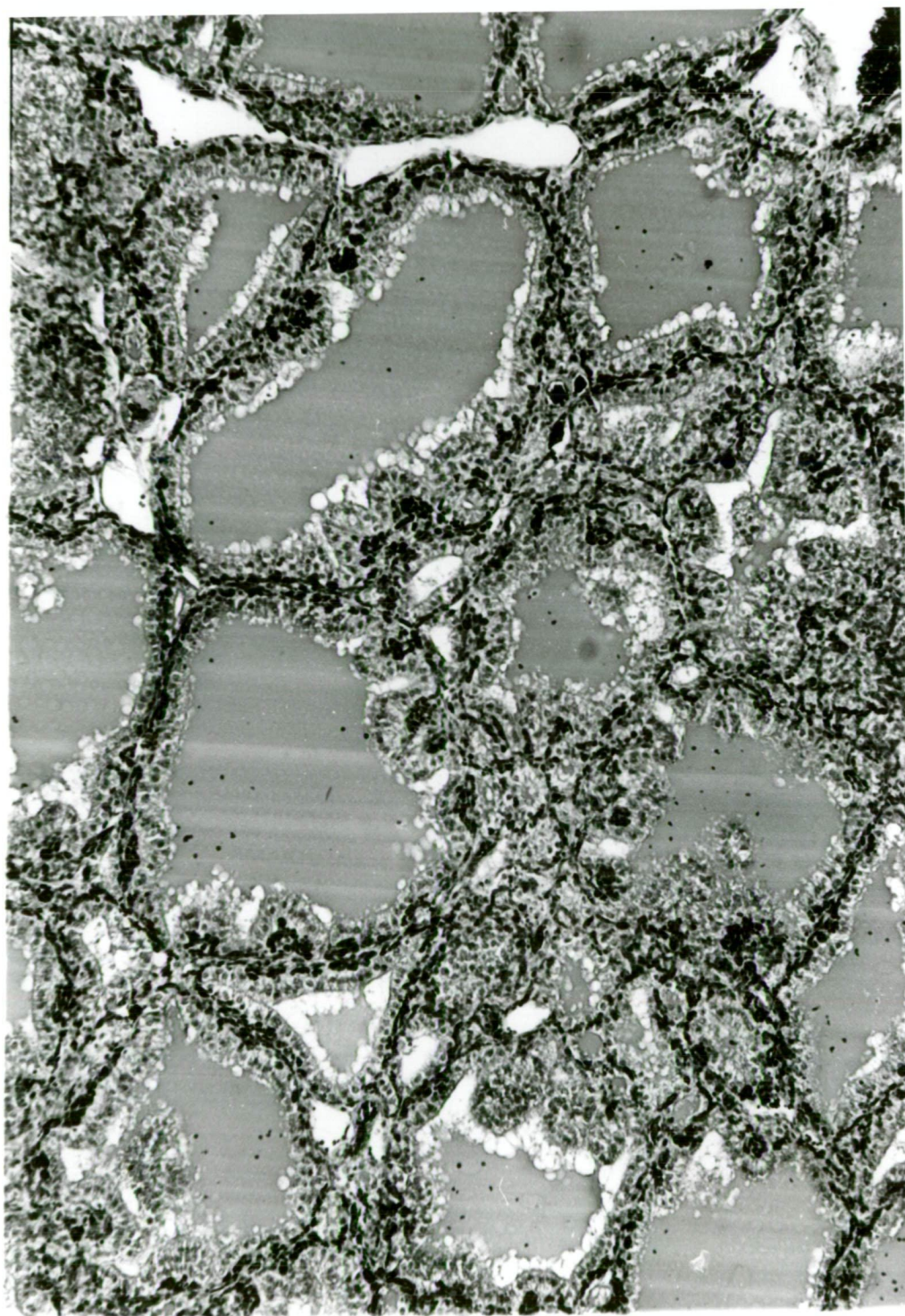


PLATE 6 - 3

THE EFFECT OF IODINE ON THYROID
HYPERPLASIA IN GOITROUS LAMBS.

A COLLOID CHANGE HAS BEEN PRODUCED.



could be fed on natural vegetation, iodine could be added when required and a high incidence of goitre had been reported in them. This goitre caused heavy losses during lambing, by stillbirth or neonatal death. The Mt. Pleasant laboratory at Prospect in Tasmania supplied me with many sections of sheep's thyroid glands for examination, and the following four figures are representative. From the studies of Marine and Lenhart these histological patterns can be correlated with iodine deficiency of varying degrees.

Plate 6 - 1 shows active hyperplasia with cells becoming columnar and the nuclei moving away from the basement membrane. There is much colloid absorption. In some follicles this is complete and very little interstitial tissue is to be seen. In Plate 6 - 2 the hyperplasia is less intense but the process is similar. The sections of iodine deficiency goitre in children and goats from the Himalayan area are very similar (Ramalingaswami 1969). If only restricted fields were examined it would be difficult to distinguish this hyperplasia from that seen in thyrotoxicosis.

The marked effect of iodine is shown in Plate 6 - 3. This was given by mouth and the lamb sacrificed after a few weeks. The dose was in excess of the requirements of the animal. The vesicles have become very large with great increase in colloid. The cells have returned to a flat cuboidal form and the whole picture has changed from hyperactivity to a resting phase. This appearance, though readily pro-

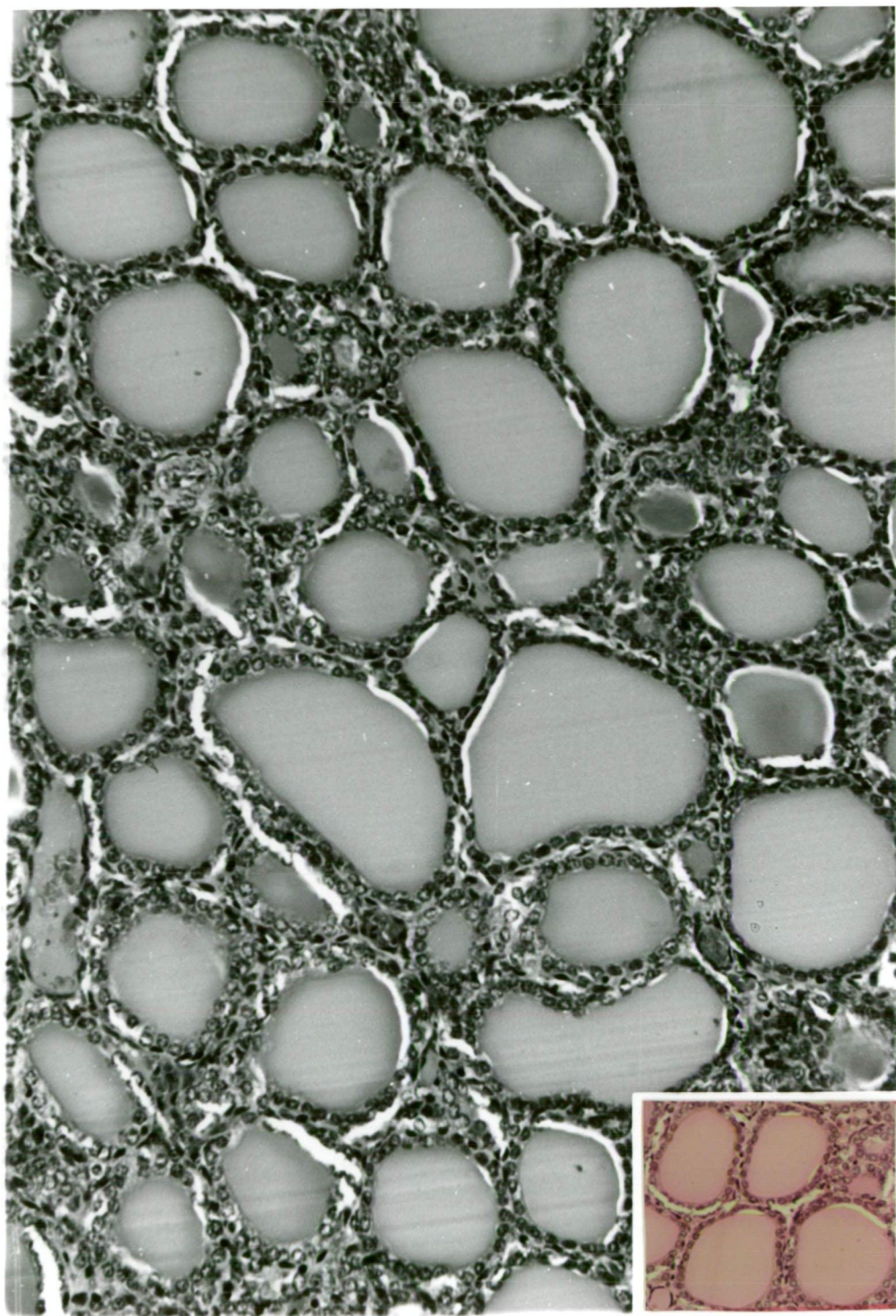


PLATE 6 - 4

NORMAL THYROID GLAND IN A LAMB WHOSE
MOTHER HAD RECEIVED IODISED OIL DURING
PREGNANCY.

duced in lambs, is never seen in human thyroid glands in Tasmania. The large smooth colloid goitres described from many areas of the world are not seen in Tasmania.

The good effect of prophylaxis with iodine in preventing loss of lambs is well known to the farmers of Tasmania. The result following one intramuscular injection of iodised oil to a pregnant ewe is shown in Plate 6 - 4. This is a section of her lamb's thyroid showing regular follicles similar in size, and lined by cuboidal epithelium filled with well stained colloid. There is a normal amount of interstitial tissue. The result is a normal thyroid pattern, with neither the resting appearance of Plate 6 - 3 nor the hyperactivity seen in Plates 6 - 1 and 6 - 2.

HUMAN NON-TOXIC GOITRE

Approximately 500 sections of thyroid have been studied. These were supplied from autopsy and operation material at the Royal Hobart Hospital (600 beds) and operation specimens from two private hospitals in Hobart (80 beds). These three hospitals serve the majority of the 200,000 people in Southern Tasmania. They were gathered over a twenty year period.

In 1968 I said of Tasmanian goitre "smooth colloid goitre does not occur; all thyroids removed contain nodules. Haemorrhage into a nodule is common. Microscopically the glandular tissue shows irregularity in the size of the acini, with compression of the surrounding tissue." (Clements 1968). These views are similar to those of De Smet, reporting the pathology of goitre from iodine deficient areas

PLATE 6 - 5

MULTINODULAR GOITRE SEEN
IN TASMANIA - LOW POWER.



PLATE 6 - 6

MULTINODULAR GOITRE SEEN
IN TASMANIA - HIGH POWER.

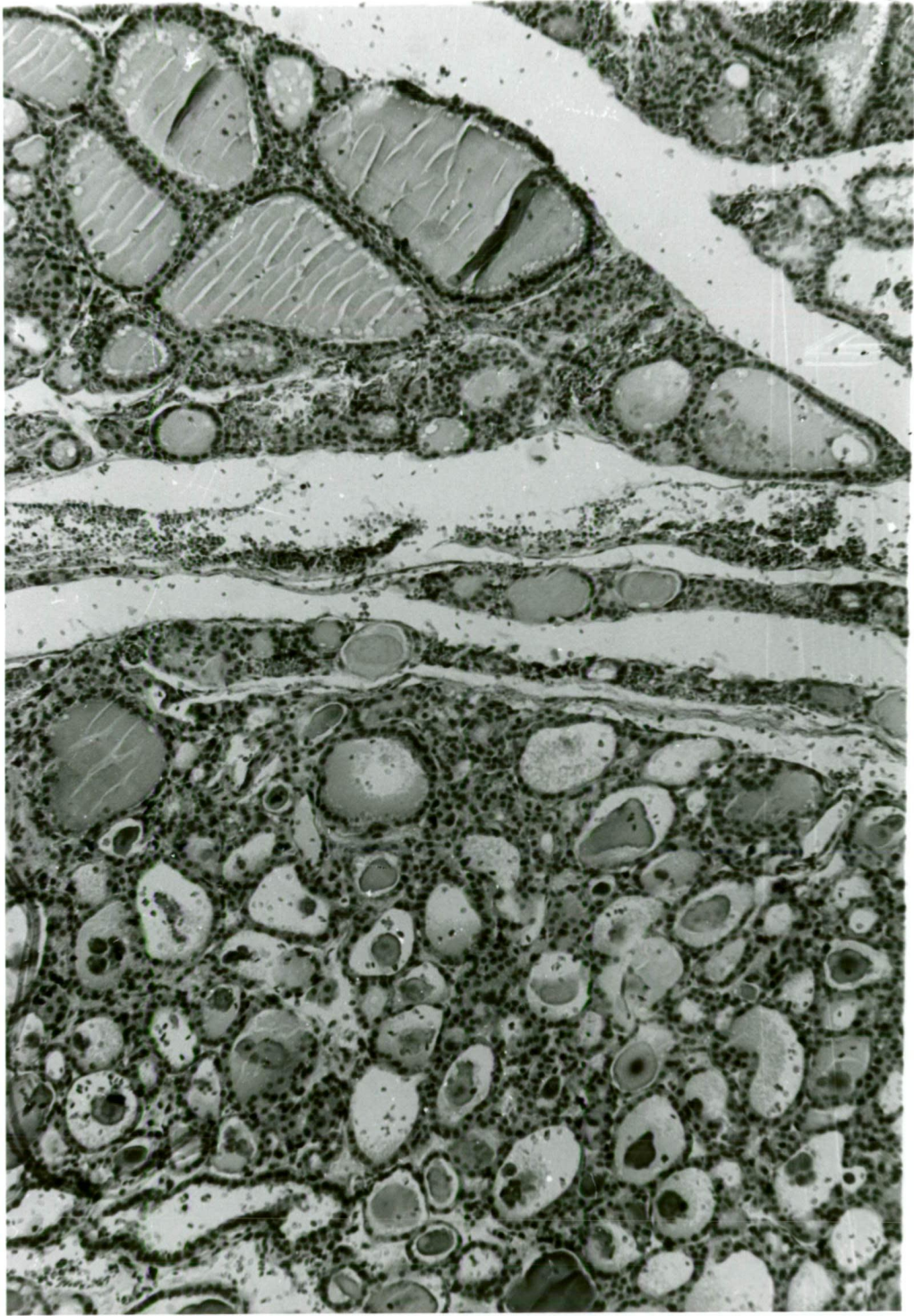
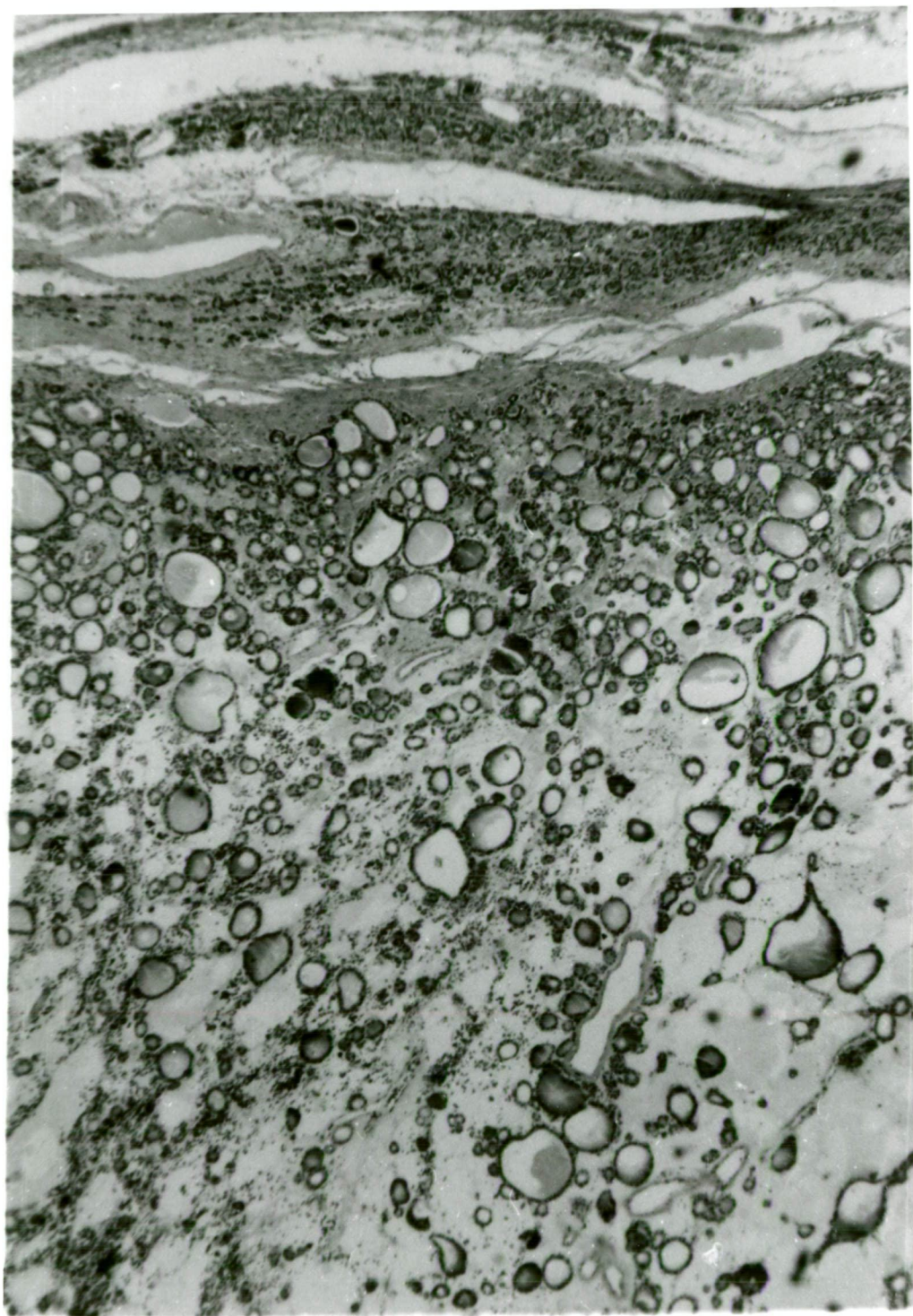


PLATE 6 - 7

MULTINODULAR GOITRE
SHOWING MICROFOLLICLES



in the Congo and elsewhere (De Smet 1960).

A typical non-toxic nodular goitre seen in Tasmania is shown in Plate 6 - 5. Varying sized follicles in groups separated by false capsules contain blood vessels. Lymphoid tissue, in places forming lymph follicles, is abundant. The whole appearance is that of varying activity with irregularity in size and shape of the developing lobules which will become future nodules. A high magnification in Plate 6 - 6 shows differing size of the follicles, the cuboidal epithelium, the compression of the follicles upon each other and the fibrous tissue forming within the planes.

Macrofollicular and microfollicular types occur. The latter is shown in Plate 6 - 7 where small follicles appear to float in a sea of clear ground substance. Haemorrhage is common and macrophages of "heart failure cell" type are seen frequently. Fibrosis replaces the absorbing blood clot which can be locally extensive, but never life threatening, in my experience. Contraction of the scar tissue produces further irregularity and deformity. Progression to calcification in these areas is common and can be demonstrated by x-ray examination of the patients, and in biopsy and autopsy material.

HUMAN TOXIC GOITRE

During investigation of thyrotoxicosis in Southern Tasmania over the past ten years, primary Graves disease with diffuse hyperplasia and smooth enlargement of the thyroid was seen only rarely. Sections from thyrotoxic patients, obtained in the first ten

PLATE 6 - 8

MULTINODULAR GOITRE WITH
EVIDENCE OF THYROTOXICOSIS

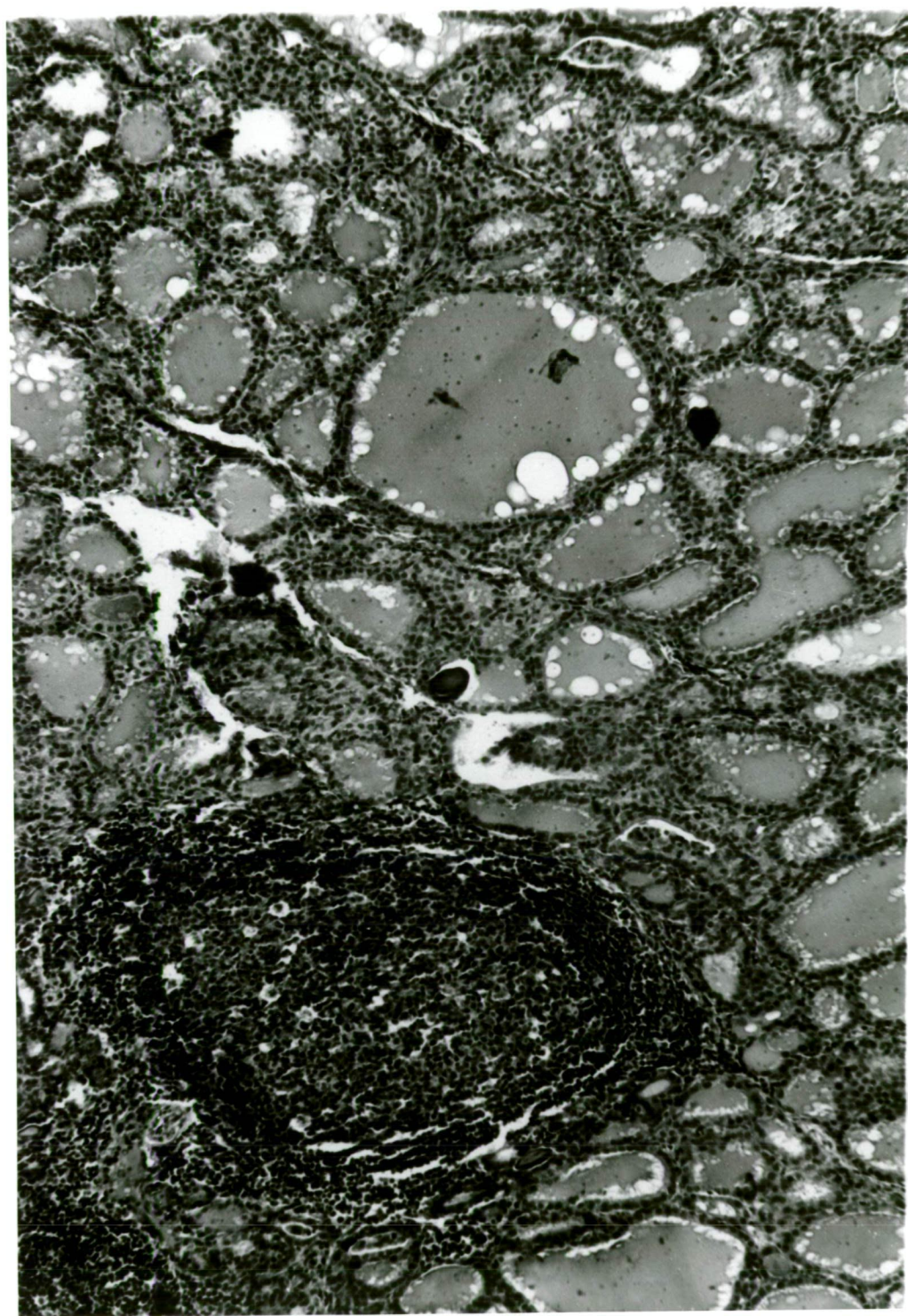


PLATE 6 - 9

TOXIC NODULAR GOITRE WITH
PSEUDOTUMOUR FORMATION



years when the clinical assessments were not documented in as much detail, are similar to those which will be seen in the next two figures. Nearly all of my cases had the histopathology pattern shown in Plate 6 - 8. Here the nodular goitre appearance is present but the cells have become more columnar, the nuclei are moving away from the basement membrane and are more densely stained. Colloid absorption is present and infiltration with small round cells even to lymph follicle formation is seen. Activity can be even more marked as in Plate 6 - 9 where hyperplasia has increased and papillary-like buds invade and absorb the colloid in the follicles. Here the invagination is quite intense giving an impression of papillary neoplasia. This is the pseudo-tumour appearance reported by Warren and Meissner. It is a not infrequent finding in toxic nodular goitres in Tasmania (Warren and Meissner 1968).

HUMAN THYROIDITIS

Biopsy and autopsy material from the same sources provided the illustrations for thyroiditis shown in the following four photomicrographs. Although infiltration with small round cells, even to the formation of lymph follicles, is a very common finding in the sections of toxic glands, generalised thyroiditis of all types has been proven in only about two to three cases per year at the Royal Hobart Hospital. It is interesting to record that sera from one hundred goitrous teenage girls contained no thyroid antibodies, whereas thyrotoxic patients gave positive results in about 30 per cent of cases. The latter result agrees

PLATE 6 - 10

SUBACUTE THYROIDITIS

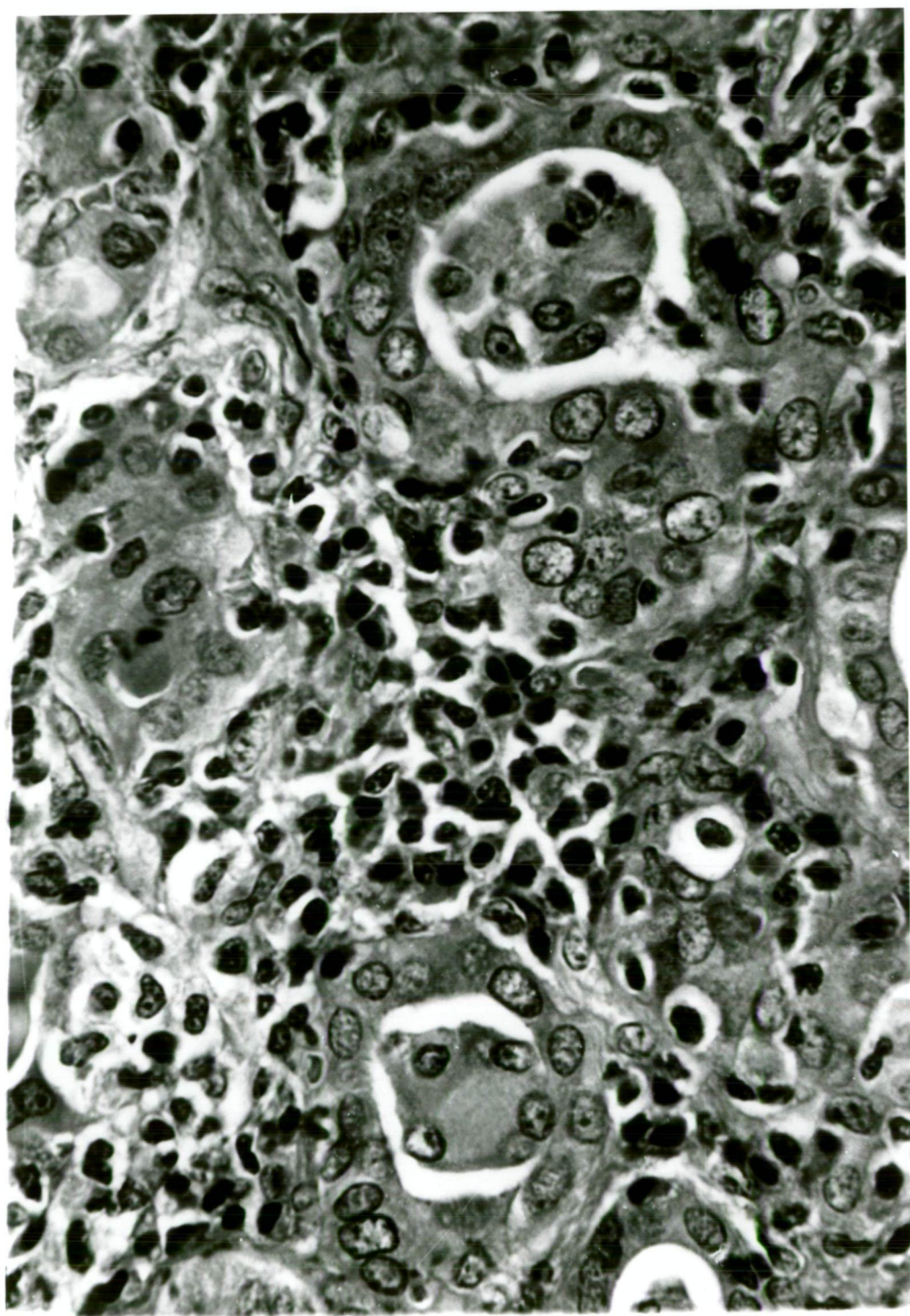


PLATE 6 - 11

GIANT CELL THYROIDITIS



PLATE 6 - 12

HASHIMOTOS THYROIDITIS

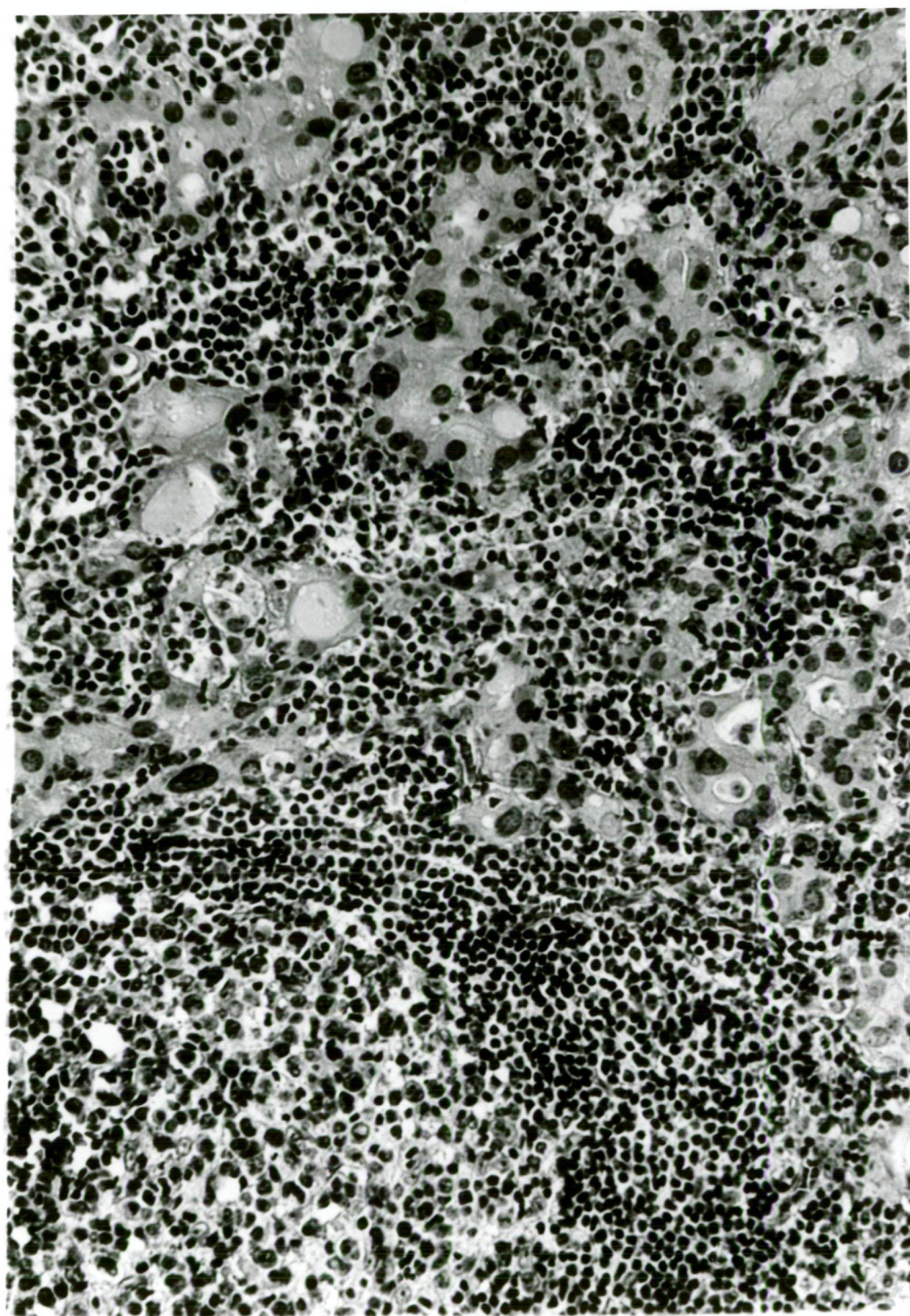


PLATE 6 - 13

CHRONIC THYROIDITIS



with figures quoted from other areas (Whittingham 1970).

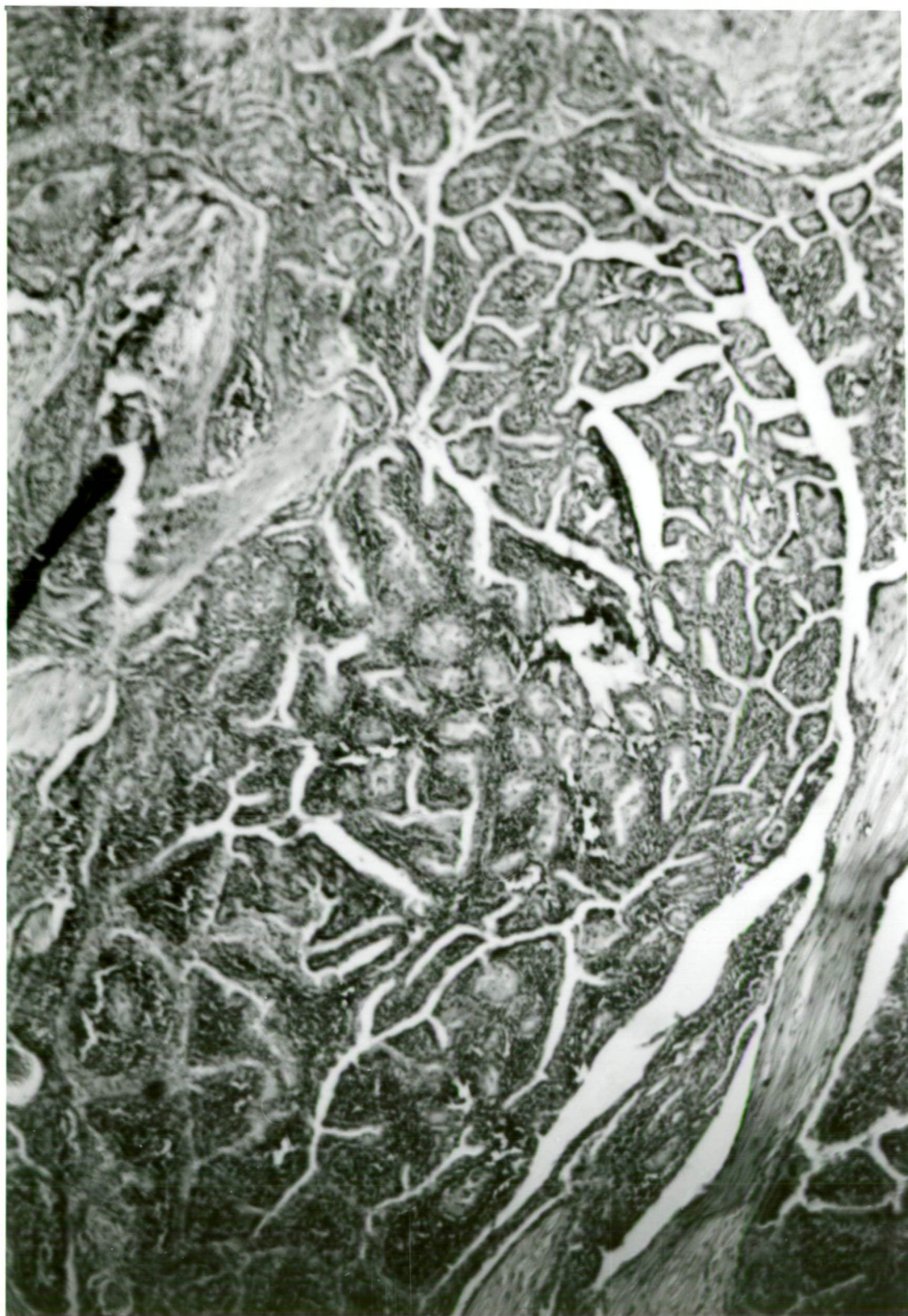
Plate 6 - 10 shows active subacute thyroiditis with invasion of stroma and follicles by lymphocytes and plasma cells. A report of one case of suppurative thyroiditis is recorded in the hospital records. This appears to have been a genuine case, but no biopsy was performed.

Plate 6 - 11 shows the classical appearance of De Quervain's "giant cell" thyroiditis. The pseudo-tubercles are prominent and no caseation is present. Giant cells are seen in the lower part of the figure. Whether these are foreign body giant cells reacting to colloid released from ruptured follicles (Ackerman 1953), or are the result of the fusion of follicular cells surrounding colloid (Anderson 1961), remains an open question. The colloid, lying free in the upper part of the picture, could be accounted for by either mechanism (De Quervain 1936).

A case of Hashimoto's thyroiditis is illustrated in Plate 6 - 12. There is generalised infiltration by chronic inflammatory cells with poorly formed and disrupted follicles containing very little colloid. One could assume decreased hormone production and secretion from such a gland. A more advanced stage is seen in Plate 6 - 13 where follicle destruction and replacement by chronic inflammatory cells is proceeding, added to which there is a large amount of fibroblastic activity with scar tissue formation which should result in complete replacement by fibrous tissue. Whether this section should be labelled Reidel's thyroiditis is an open one (Hashimoto 1912, Reidel 1896).

PLATE 6 - 14

PAPILLARY CARCINOMA



The majority of the sections of thyroiditis have come from biopsy and autopsy material from patients suspected of having this condition. Thyroiditis has been found also in routine sections of toxic and non-toxic goitres where the condition was not suspected preoperatively. One such example in a thyrotoxic patient proceeded to myxoedema requiring permanent thyroxine therapy.

HUMAN THYROID CANCER

The commonest form of thyroid cancer is the papillary carcinoma seen in Plate 6 - 14. As in other centres, the few cases documented in Tasmania occur in females in the 20-50 year age group. Cancer may be found by chance at thyroidectomy for thyrotoxicosis or non-toxic goitre. The total number of thyroidectomies, for thyrotoxicosis in Southern Tasmania, is not sufficient for a significant figure to be given but the few cases which have occurred suggest an incidence of 1 per cent, similar to that quoted by other writers (Olen and Klinck 1965). In Tasmania, as in other areas of the world, papillary carcinoma is a relatively benign condition and life expectancy is excellent, approaching the survival rate of the general community (Lindsay 1969).

In Hobart, the opposite applies to all the medullary and anaplastic carcinomata which occur in the elderly: whether treated by surgery, radiotherapy or both. The mortality rate for those seen has been 100 per cent within a few months of diagnosis. One is led to the belief that present treatment has little effect in this group. A prognosis intermediate

between papillary carcinoma on the one hand, and anaplastic and medullary carcinoma on the other, could be given for the few cases of follicular carcinoma seen in Tasmania. Variability of type within the same section of thyroid carcinoma was seen and a definite classification of each individual cancer could not be given.

Two examples of Hürthle cell carcinoma were found during the 20 year observation period. The rare haemangioendothelioma which appears to be confined to Switzerland was not encountered, nor were there any cases of sarcoma.

CHAPTER 7

RELATIONSHIP OF ENDEMIC GOITRE TO CANCER AND THYROTOXICOSIS

Since Tasmania has been an area of endemic goitre for many years, with a goitre prevalence of 30 per cent in adult females over forty, any relationship of this condition to cancer or thyrotoxicosis, is of great importance.

CANCER

INTRODUCTION

This disease was first described by Burns in his book "Observations on the Surgical Anatomy of the Head and Neck" (Burns 1811). Many conflicting reports regarding the incidence of cancer have appeared and it has been said "Cancers are more frequently found in regions in which interest in the disease is high" (Winship and Rosvoll 1969). The incidence of cancer, found at routine autopsy was 0.08 per cent but this rose to 1.79 per cent if the thyroid received special attention (Studer 1969).

Ackerman, quoting Horn, Ward, Crile and Cole, gives incidences of cancer in nodular goitre between 10 and 17 per cent. Crile and Cole stated that 25 per cent of solitary nodules contain cancer (Ackerman 1953). These were clinical assessments by the surgeons mentioned. A contrary opinion is held by Kambal reporting an incidence of cancer of less than 2 per cent in solitary nodules in Khartoum (Kambal 1969). In Tasmania, where multinodular goitre is found most frequently, and where one nodule increases in size more than all others, a clinical diagnosis of solitary nodule could be made. At operation however, solitary nodules are rarely found.

PLATE 7 - 1

REPRESENTATIVE THYROID SCANS

1. MULTINODULAR GOITRE WITH COLD NODULES
2. INCREASED ACTIVITY
3. NORMAL THYROID SCAN
4. HOT NODULE
5. LARGE MULTINODULAR GOITRE WITH HOT AND
COLD NODULES
6. MULTINODULAR GOITRE

1



4



2



5



3



6



Thyroid scanning gives some help in the diagnosis of multinodularity. I have performed more than 500 thyroid scans and examples are given in Plate 7 - 1. On the other hand the use of caesium - 131 to distinguish neoplasms from nodular goitre in Tasmania though promising (Murray 1970) is not accurate enough in my hands at the present time.

In experimental animals, iodine deficiency when combined with goitrogens, produces hyperplasia which proceeds to neoplasia, in a statistically significant proportion (Doniach 1969, Purves 1946). Some workers have produced neoplasia by iodine deficiency only (Beirwaltes 1966). It has been shown that the iodine deficient thyroid not only increases T.S.H. secretion by its failure to supply enough thyroxine and triiodothyronine, but such a gland is more sensitive in its response to T.S.H., hyperplasia being greater than in a normal gland (Burke 1970). Nevertheless, no direct relationship has been shown to occur in man. Although cancer occurs in iodine deficiency goitres, inborn errors of thyroid metabolism, peroxidase defect goitre, familial goitre and Pendred's syndrome, the incidence may be significant but equally may be a chance phenomenon. Selective reporting of cases in which cancer and these conditions occur may give a false impression (Stanbury 1969).

CANCER INCIDENCE

Cancer rates have been reported from many areas of the world. In Italy, 43 carcinomata were found in 1816 cases of goitre coming from an endemic area. Three were recognised preoperatively (Frasson 1962).

In Switzerland, although goitre prevalence has dropped considerably since iodised salt has been used, the cancer rate particularly in younger people, has not changed. On the other hand, the more highly malignant tumour incidence, occurring in the elderly has fallen (Walther 1963). Ramalingaswami suggests that papillary tumours are unrelated to endemic goitre, but anaplastic and follicular tumours are related (Ramalingaswami 1969). One might expect that with increased diagnostic ability the reported cancer rate might have risen slightly over recent years. Thyroid cancer incidence is the same in the goitrous Birmingham, Alabama, and non-goitrous Dallas, Texas. Reduction in goitre incidence has been followed, after some years of increase, by a decrease in mortality from thyrotoxicosis but death rate from cancer shows a slight increase over the period, as seen in Figure 7 - 1 (Pendegrast 1961). Any close relationship between cancer and goitre incidence should have produced a falling cancer rate. This is not shown in Figure 7 - 1.

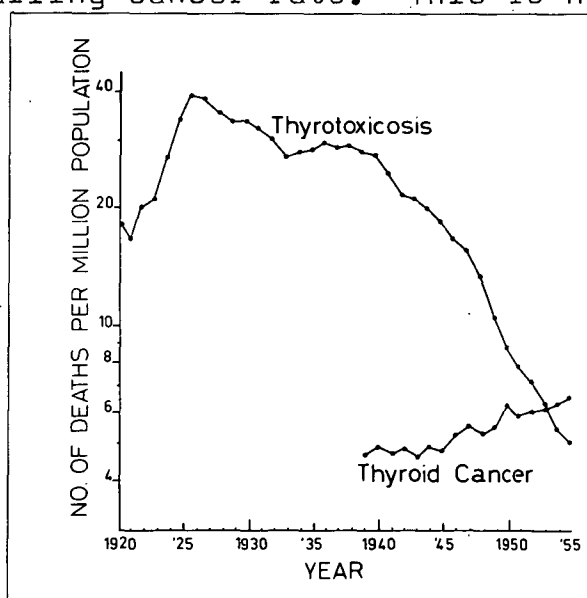


TABLE 7 - 1

CUMULATIVE	SURVIVAL	RATES
PAPILLARY	CARCINOMA	OF
THYROID		

10 YEARS	84 PER CENT
20 YEARS	63 PER CENT
30 YEARS	58 PER CENT

(LINDSAY 1969)

Neither Saxén in Finland nor Walthard in Switzerland could confirm any increased incidence of cancer in goitrous regions (Saxén 1950, Walthard 1960). It should be noted however that although the goitre prevalence has fallen in Switzerland, radioiodine uptakes remain high, suggesting that prophylaxis is still inadequate, and thyroid cellular activity remains increased even though gross, i.e. clinically detectable enlargement may not occur (Studer 1969). The lack of a direct relation between goitre prevalence and cancer of the thyroid, in various parts of the world was reported by Hakama, Pedersen, Ramalingaswami and Furihata in 1969.

Several authorities suggest that the varying incidences are more apparent than real, due to inadequate case finding. They give an incidence of 10-20 per million population per year, and state that thyroid cancer incidence is less than one per cent of all cancers (Hakama 1969, Perinetti 1969).

A prospective study by Vander and others was begun in 1948. In 5127 subjects, aged 30-50 years with approximately equal numbers of males and females, 218 had nodular goitre. Over a twenty year period, no case of overt cancer of the thyroid was found. They conclude that thyroid cancer rarely develops in nodular goitre - a view shared by Astwood - and that it is very rare in the population at large (Vander 1968, Greer and Astwood 1953).

Crile and Dempsey stated that, without better definition of histological criteria, better autopsy and clinical statistics, it was impossible to make

an accurate statistical report of the true incidence of thyroid cancer in nodular goitre. They point out that although histologically malignant tissue is found as a surprise at autopsy or operation, these lesions are very benign and do not cause any harm, over many years (Crile and Dempsey 1949). Support for this view comes from cumulative survival rates for the common form, papillary cancer, given in Table 7 - 1. These figures are no different to survival rates in the 30-50 year age group in the general community. Follow up data on 1181 cases of thyroid cancer by Woolmer (1968), supports this view. He showed that for the common type (papillary) where the lesion was found accidentally, or was confined to the thyroid gland, at surgery the 50 per cent survival rate equalled 32 years and was exactly the same as that for a matched series from the general population. Even with spread outside the gland the 50 per cent survival rate was 16 years. In contrast the rare anaplastic carcinoma of the elderly had a 50 per cent survival rate of six months. Piercey (1968) gives further support to the opinion of the overall benign nature of the condition. He divides the cancers into three types:

1. Obvious cancer in old age; rare but with a very bad prognosis.
2. Clinically suspected cancer in middle age with a good prognosis.
3. Clinically hidden and found accidentally with an excellent prognosis.

TABLE 7 - 2

THYROID	CANCER	INCIDENCE
TYPE	CLINICAL INCIDENCE	CANCER SURVEY
ANAPLASTIC	25 per cent	6 per cent
FOLLICULAR	25 per cent	18 per cent
PAPILLARY	50 per cent	76 per cent

Further confusion, in assessing the incidence of the disease, is illustrated by Saxén and others in Table 7 - 2. The three commonest types of carcinomata of thyroid, vary in incidence depending upon the method of collecting the information about them. The clinical incidence in a community or a special cancer survey giving different incidences are shown (Saxén 1969).

The relationship between cancer of the thyroid and thyrotoxicosis is more definite than with endemic goitre. A high incidence of thyrotoxicosis and cancer of the thyroid in the presence of low endemic goitre prevalence has been reported from Iceland (Hakama 1969). Olen and others reported an overall cancer incidence of 2.5 per cent in sections from 2114 glands removed for thyrotoxicosis. They reported an incidence of 1 per cent for papillary cancer in this disease (Olen and Klinck 1965). Collier reported from autopsy material that nearly half the carcinomata were associated with hyperthyroidism (Collier 1929), but the pseudo tumours occurring in thyrotoxicosis, defined later by Warren and Meissner should be remembered in this context. Nevertheless, there appeared to be some association between thyrotoxicosis and cancer. In 1954, Sokal organised a door to door canvas of a carefully selected sample of a population of 2,500,000 in the U.S.A. in one study year. The results of this study can be summarised as follows:

1. Thyroid cancer arises more frequently in toxic than non toxic goitre.

2. 1 per cent of toxic nodular goitre contain malignant tissue.
 3. Sex ratio for cancer is the same.
 4. Lifetime risk for patients with nodular goitre is less than 1 per cent.
 5. There was no evidence for the increased incidence of cancer in solitary nodules (Sokal 1954).
- These views were shared by Clements (Clements 1954).

A curious report from Roumania completes this review. Petrea reported areas on the Black Sea coast where iodine consumption is high (200-400 ug/day) 60-80 per cent of children and 15-20 per cent of adults are goitrous. He gave no figure but stated that the incidence of cancer of the thyroid was high. I have written to this worker on several occasions asking for further information but to date have had no reply. No further evidence of this very curious occurrence has been presented in current literature (Petrea 1969).

STUDIES IN SOUTHERN TASMANIA

In Southern Tasmania I have gathered all cases of cancer presenting clinically over the past fifteen years. The sources of these cases have been biopsy and autopsy material, sections of thyroid glands removed surgically for toxic and non toxic goitre and case records from The Peter MacCallum Clinic which is the sole radiotherapy unit in this region. Those found by chance in routine autopsy of people dying from other diseases are not included. They represent thyroid cancers giving clinical symptoms referable to the thyroid gland and are comparable to the incidences

TABLE 7 - 3

ANNUAL INCIDENCE OF THYROID
CANCER PRESENTING CLINICALLY
IN SOUTHERN TASMANIA

YEAR	FEMALE	MALE	TOTAL
1957	1	1	2
1958	2	1	3
1959	1	0	1
1960	1	0	1
1961	1	0	1
1962	3	0	3
1963	2	0	2
1964	0	1	1
1965	1	0	1
1966	1	0	1
1967	3	1	4
1968	1	2	3
1969	1	2	3
1970	1	0	1
1971	2	0	2
15 YEARS	21	8	29

quoted above from Hakama, Perinetti and Fridman. I have checked personally, all the sections and found no examples of pseudo-tumour among them. There have been 29 cases over the past fifteen years. These are shown with their annual incidence and sex ratios in Table 7 - 3.

Admittedly the numbers are small, but in a population of 200,000 the incidence of cancer presenting with symptoms referable to the thyroid gland is approximately two per year, or 10 per million population, equal to that expected from world figures. The sex ratio in this series is $F : M = 2.6 : 1$.

Thus cancer in Southern Tasmania, is an uncommon disease, its incidence being at the lower level of the range of world figure of 10-20 / million. However the most accurate cancer rates have been determined from goitrous areas and some non-goitrous countries may have lower rates. On the other hand it has been shown on Page 114 that there is no direct correlation between goitre and cancer incidence in several countries. There has been no marked change in thyroid cancer presenting clinically in Southern Tasmania over the fifteen year period shown in Table 7 - 3.

THYROTOXICOSIS

Several reports emphasise the close link between endemic goitre and thyrotoxicosis, and a causal relationship has been suggested by Matovinovic in Yugoslavia, Stanbury and Pendegrast in U.S.A. and Hetzel in Australia (Matovinovic 1958, Stanbury 1958, Pendegrast 1961, Hetzel 1971). Wyndham reported an association between toxic nodular goitre and endemic

goitre in N.S.W. Australia, but criteria for diagnosis could be questioned (Wyndham 1940). He showed an increasing mortality rate from thyrotoxicosis in Australia, beginning about 1934 and in Britain beginning about 1925. The increasing rates are similar to those found in the U.S.A. in the period 1920-1940 (Figure 7 - 1) by Pendegraft who gives other supporting evidence for increased incidence of thyrotoxicosis associated with endemic goitre. On the other hand Campbell was unable to show a close connection between endemic goitre and exophthalmic goitre and he was supported in this view by Berry and McCarrison (Campbell 1924). Other reports from goitrous areas of Britain are not completely convincing as the studies are retrospective and the diagnoses were entirely clinical. Investigators of endemic goitre report no increased incidence of thyrotoxicosis in South America (Stanbury 1970), in New Guinea (Choufoer 1963, McCullagh 1963, Buttfield and Hetzel 1967), in India (Sooch and Ramalingaswami 1965), or in Africa (Ermans 1969, Delange 1969). De Smet was unable to find any evidence of thyrotoxicosis, in over a thousand sections of goitrous thyroids which were excised in the Congo (De Smet 1960). In Tasmania three examples of thyrotoxicosis were found in a series of 1000 thyroidectomies for multinodular goitre (Pryde 1958). Unfortunately none of these workers have given absolute incidence figures for thyrotoxicosis in the countries mentioned, nor are figures available in the literature.

In Tasmania, gradually increasing incidences of thyrotoxicosis in the Northern half of the State (Stewart, Vidor and Hetzel 1971) and for the South (Connolly 1971) have been reported. The rate rose from a low incidence of approximately 10 per 100,000 per year in 1960 to approximately 18 per 100,000 per year in 1965. Inferences drawn from death rates which present a contrary view (Clements 1959), are not valid in my view, in that they are drawn from death certificates. Groups of such certificates were obtained from Tasmania, Victoria, N.S.W. and Queensland. I found them to be very inaccurate and in several cases thyrotoxicosis, cured many years previously, was included in the cause of death and recorded by the Registrars of the States as death from thyrotoxicosis. Thus there is no good evidence to 1965, to suggest that endemic goitre was associated with an increased incidence of thyrotoxicosis in Tasmania. With an overall goitre prevalence of 30 per cent in adult females at that time and an incidence of thyrotoxicosis F : M of 5 : 1 approximately (Connolly 1970), a causal role, if any, for endemic goitre producing thyrotoxicosis must be of very minor degree. Such a low incidence of thyrotoxicosis, requiring a population pool of many thousands to produce a few cases, is probably the reason for the lack of reports of the disease from the various areas, particularly in the developing countries where, at most, a few thousand subjects were studied.

The diagnostic criteria before 1950 in Tasmania cannot be relied upon. Diagnosis was a clinical one

without laboratory confirmation. Antithyroid drugs, which lowered the mortality rates in medically and surgically treated patients, were not available. Hospital records up to this time, were very inadequate in Tasmania. In one series an incidence of thyrotoxicosis equalling 50 per cent of nodular goitre is given (Pryde 1944). The very large numbers of thyroidectomies carried out in the period 1930-1950 on the clinical diagnosis of thyrotoxicosis contribute to this false impression, and to the increase in mortality rates from the disease (Gaha 1951).

It can be said for Tasmania, that there is no certain evidence to show that, until 1965, endemic goitre was associated with any increased incidence of cancer or thyrotoxicosis. Indeed evidence will be produced to suggest that the incidence of thyrotoxicosis may have been less than the average world figures before 1960.

CHAPTER 8

IODINE PROPHYLAXIS
IN
TASMANIA

INTRODUCTION

In 1905, Tasmania introduced a school medical service, being the first State in the Commonwealth of Australia to do so. Reports, from this body and from private practitioners, confirmed the continuing high incidence of goitre in children and adults. Anderson who practiced medicine for 23 years in the Huon Valley, South of Hobart, reported a high incidence of goitre. He believed that bacillus coli was the cause and that calcium might be involved. He noticed that goitres occurred irrespective of the source of water supply, whether from iron tanks filled by rainwater, wells or streams (Anderson 1914). Reports from the school medical service in 1916, 1918 and 1919 give high goitre rates, and a goitre survey among school children was planned in 1922 (Public Health Reports). Morris reported a series of 644 large goitres, 575 in female and 69 in male adults. He reported 149 large goitres in children (Morris 1923).

Unfortunately, there occurred in Tasmania about this time what has been called the "Great Dispute" between the British Medical Association and the Government of the State. "The years of dispute lasted from 1917 to 1924 in Launceston but continued in Hobart until the 1930's. During this period the Hospital Boards had great difficulty in obtaining staffs" (Craig 1963).

The Hobart General Hospital became a closed one, with a surgeon superintendent - Dr. V. R. Ratten. This man's qualifications were seriously questioned, and to allow him to continue to run the hospital,

a special Act of Parliament was passed registering him in Tasmania (1918, 1919). He was an extremely competent surgeon, but knew little, if any, pathology. No records were kept, but most of the goitres were removed surgically. Clements has shown that the mortality rate for the clinical diagnosis of thyrotoxicosis was higher in Tasmania than in the rest of Australia. It is recorded that most anaesthetics for major surgery were given by the Matron, as no anaesthetist was available (Goddard 1963).

The school medical service did not report actual goitre prevalence in children from 1925 to 1930, when it was disbanded (Med. J. Aust. 1930), possibly due to the economic depression of that time. It was not reestablished until after 1940. Thus no reliable records of goitre prevalence in children or adults is available from the early 1920's to the 1940's in Tasmania.

GOITRE IN SCHOOLCHILDREN 1949

The problem of goitre in school children was again brought to the notice of the Government of Tasmania and in 1948 the Minister for Health requested, through the Commonwealth Minister for Health and Social Services, that "Arrangements could be made for Dr. Clements to visit Tasmania at a suitable time to discuss the inauguration of a campaign against endemic goitre in this State, with officers of my Department and the Subcommittee on Goitre of the British Medical Association." (Clements 1949). Conclusions by Clements after a survey are as follows:

1. This survey of 8,934 school children between

the ages of 5-18 years revealed that most of Tasmania is an endemic goitrous area.

2. The incidence is higher in girls than boys and rises with age. Approximately 20 per cent of girls over 12 years of age had a visibly enlarged goitre and another 30 per cent palpable enlargement.

3. About 20 per cent of the teachers and student teachers under the age of 21 years had a visibly enlarged thyroid gland (Clements 1968).

It has been shown in previous chapters that natural iodine deficiency was the main, if not the only cause for the development of goitre in Tasmania. That the deficiency was moderate can be gauged by the results of urinary excretion of iodine and protein bound iodine estimations. Protein bound iodine in 100 adolescents seen in Table 8 - 1 shows no significant difference between goitrous and non-goitrous, and Figure 8 - 1 shows similar levels in 48 goitrous and non-goitrous young women aged 20 approximately, also within the normal range (3.5 - 7.5 per cent). These levels differ from patients in the New Guinea highlands where iodine deficiency is severe, many being below the lower limit of normal (Buttfield and Hetzel 1967). Urinary iodine / creatinine ratios shown in Figure 8 - 2 reveal iodine excretion below the normal for the majority. As can be seen in Figure 8 - 3 the degree of deficiency was moderate, similar to that of the New Guinea coast and Venezuela, less than the normal (Adelaide, Australia) and greater than the severe deficiency of the highlands of New Guinea. This degree corresponds with Follis's Category 111

TABLE 8 - 1

PROTEIN BOUND IODINE
100 FEMALE ADOLESCENTS

	PROTEIN BOUND IODINE	RANGE
GOITROUS	4.85 mcg.	4.0 - 5.7
NON-GOITROUS	5.35 mcg.	4.1 - 7.0

FIGURE 8 - 1

PROTEIN BOUND IODINE
48 TRAINEE NURSES
HOBART 1968

FIGURE 8 - 2

URINARY IODINE / CREATININE
ADOLESCENT GIRLS
TASMANIA 1960

FIG 8-1

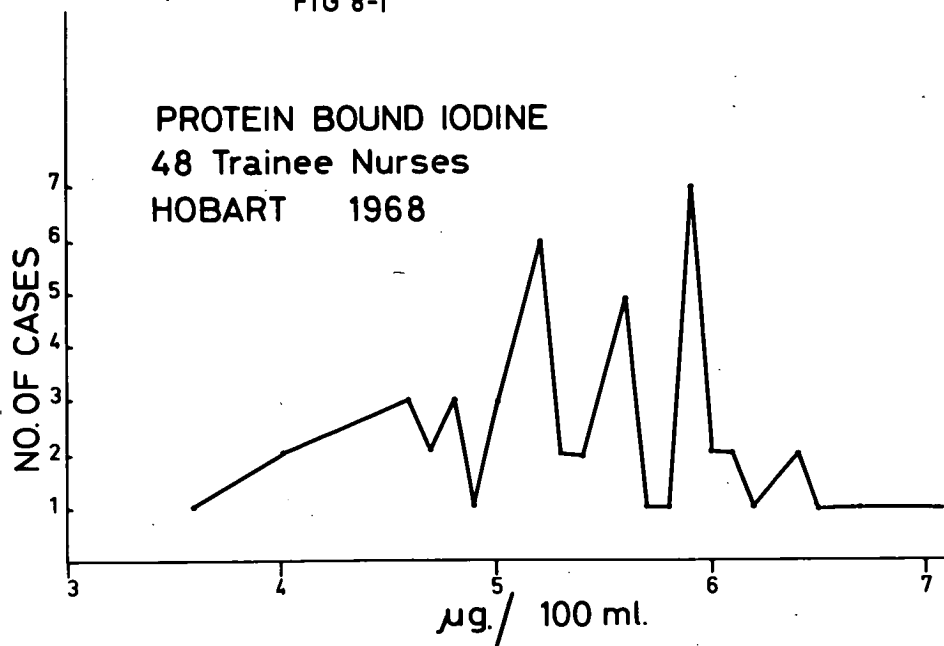


FIG 8-2

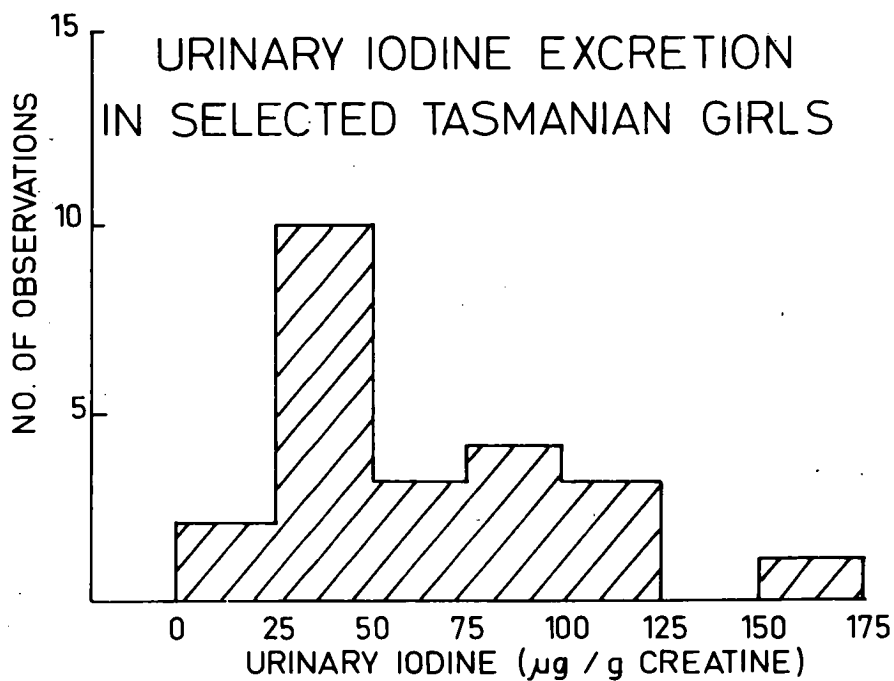
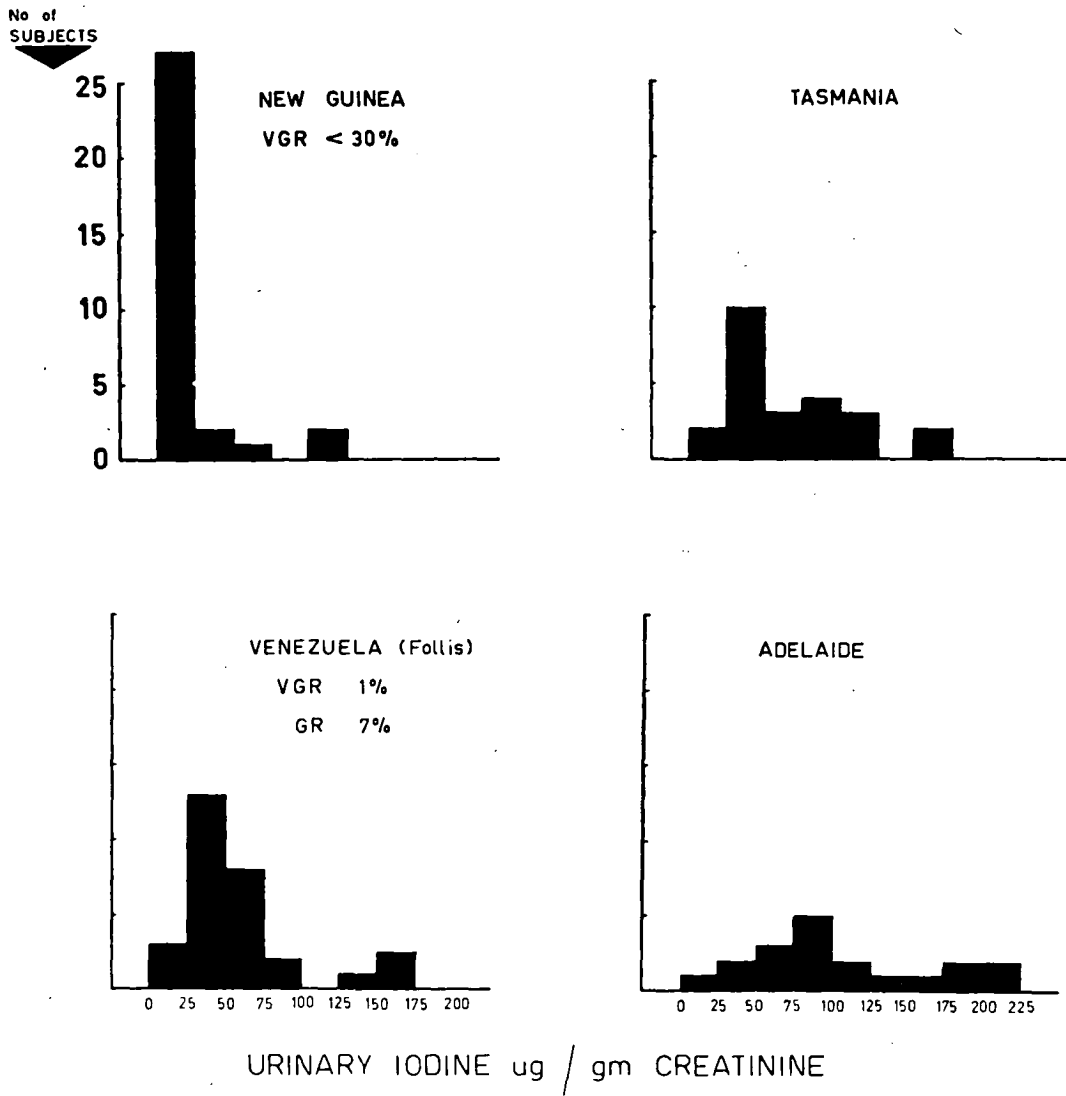


FIGURE 8 - 3

URINARY IODINE / CREATININE
NEW GUINEA
TASMANIA
VENEZUELA
ADELAIDE

V.C.R. - Visible Goitre Rate

FIG 8-3



(Follis 1964).

IODINE PROPHYLAXIS

(1) SCHOOLCHILDREN

Because the mandatory use of iodised salt was unacceptable, the method chosen for iodine prophylaxis in infants, preschool and school children was the addition of 10 mgm. of potassium iodide given in tablet form at weekly intervals. The tablets were distributed through schools and child health centres (Clements 1970). Further surveys of children in Tasmania were carried out in 1954, 1960 and 1965. They showed a steady decline in most areas but in some schools distribution was faulty, the goitre prevalence remaining high there. The prophylaxis was largely ineffective for infants and preschool children, because of their irregularity of attendance.

Even if this form of prophylaxis was completely successful, it applied to school children only, whereas the environment at this time was considered to be moderately deficient for the whole community. The visible goitre prevalence in girls aged 15-17 years was 3.7 per cent in 1960, and 3.5 per cent in 1965 (Clements 1968), but an increase occurred when these children left school. I examined 51 trainee nurses aged 19-20 years in 1965 and observed 17 with visible goitre.

Thus the tablets were ineffective before school age, partially effective during the school period, and no continuing prophylaxis was provided after this. From the examination of the nurses, it appeared likely that in adult females, the goitre prevalence would

remain at 33 per cent.

IODINE PROPHYLAXIS

(2) THE COMMUNITY

In a previous chapter, the relative merits of other prophylactic measures were discussed. Iodation of water is wasteful in that little of it is ingested. Reports from New Zealand suggest that iodised salt unless mandatory, even though widespread in its use is not completely effective, and the amount consumed by infants and small children is insufficient to provide adequate iodine supplement. A more recent report from Finland reveals that iodised salt 1/100,000 has a good effect on young schoolchildren but fails to prevent goitre during adolescence. Nevertheless this may be only temporary if the urinary iodine excretions remain at the acceptable level quoted by the authors. Their results are shown in Table 8 - 2. Other additions to the iodine environment would seem necessary to account for the rise of urinary iodine excretion by the amount shown in this table.

The successful result from iodised bread in Holland and its use in Canberra, Australia, prompted the recommendation that this be the form for universal prophylaxis in Tasmania. This was achieved very simply. A bread improver - potassium bromate - is an essential ingredient in commercial bread making. The whole State of Tasmania obtained this material through one source and this firm agreed to substitute enough potassium iodate in their improver, so that there would be a concentration of iodide of 2 parts per million dry weight of flour. This was well

TABLE 8 - 2IODINE STUDIES AND GOITRE
PREVALENCE IN FINLAND

TEST	1959	1969
^{131}I UPTAKE AT 24 HOURS	60-70 per cent	30-34 per cent
URINARY IODINE OUTPUT IN 24 HOURS	45-60 mcg	219 mcg
CHILD GOITRE PREVALENCE	15-30 per cent	1-6 per cent

(LAMBERG 1970)

below the concentration of 20 parts per million approved by the National Health and Medical Research Council in 1963 (Clements 1970). Bread surveys by the Commonwealth Bureau of Census and Statistics and by J. Howeler-Coy in Tasmania, suggested an average intake of 1500 Gm. of bread per week, giving a daily intake of 150 mcg. of iodine when the changed improver was used. This represents on average four slices per day, with a range of iodine intake from bread of 50-250 mcg. daily for males and 50-150 mcg. daily for females. All bread in Tasmania was iodated by the end of April 1966 (Howeler-Coy 1968).

Repeated examination of bread from Tasmania since 1966 showed no great variation, each slice of 100 gm. providing approximately 35 mcg. of iodine. This is in contrast to the large and varied concentrations reported from the U.S.A. where values of 150 mcg. per slice are found commonly, some reaching 1600 mcg. (Blum and Eisenbud 1967, Pittman and Chandra 1971, Sachs, Siegel, Horwitt, Siegal 1972). In some of these areas the contribution from bread alone is sufficient to reduce radioiodine uptakes as reported by these workers. The method of bread baking in the U.S.A. is different to that employed in Tasmania. In that country iodine in bread making is being replaced by azodicarbonamide, a non-iodine containing substance. This is for commercial, not medical, reasons.

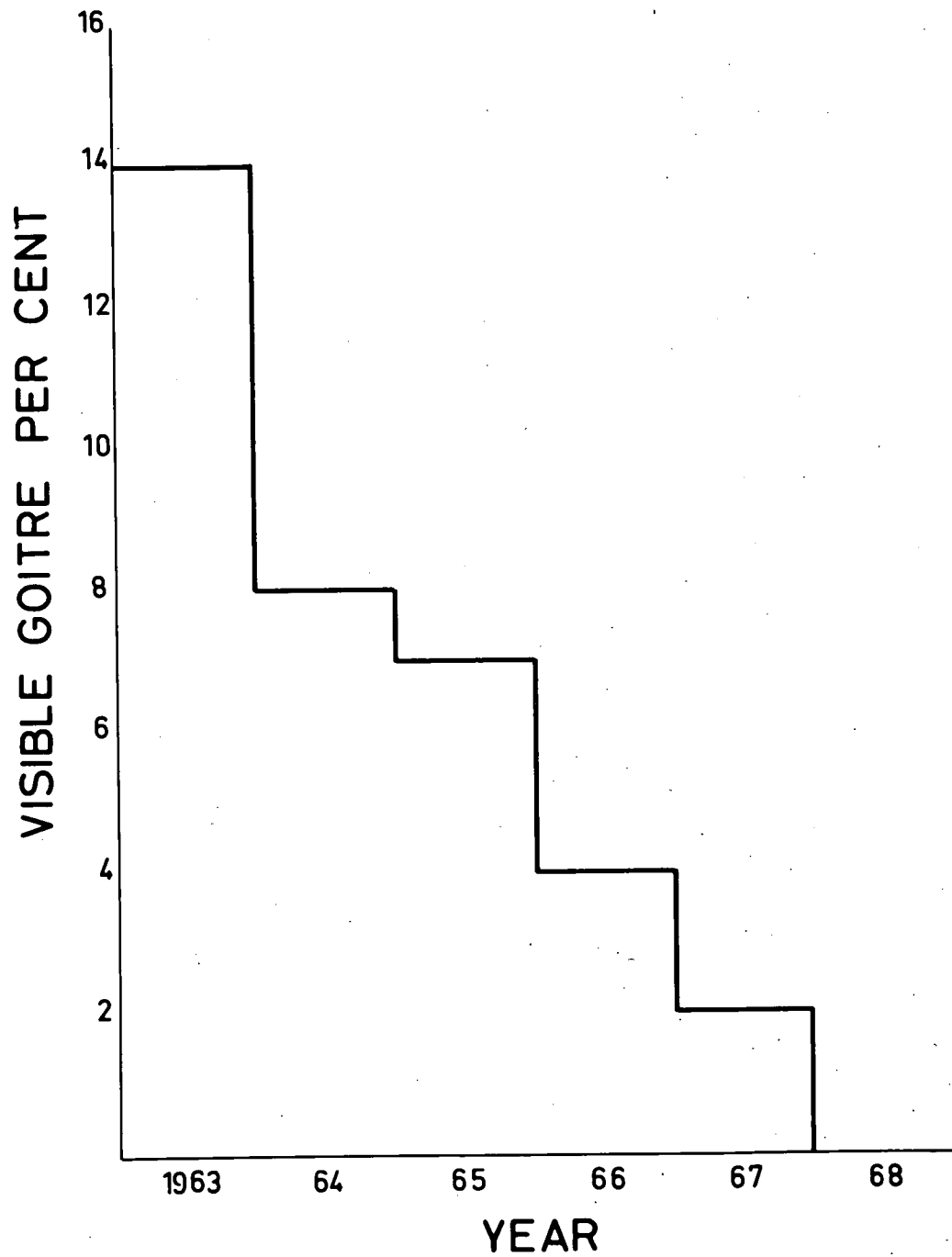
A survey of schoolchildren, in 1969, showed a marked drop in the standardised prevalence rates for goitre when compared with the previous surveys. Whereas up to 1965 a steady fall was occurring in some areas,

FIGURE 8 - 4

GOITRE INCIDENCE IN SCHOOL ENTRANTS
HUON VALLEY
1963 - 1968

FIG 8-4

HUON VALLEY SCHOOLS
ENTRANTS 1963-1968



in 1969 the prevalence rates were overall about equal to the rates in a non-goitrous area. Figure 8 - 4 shows that children entering school for the first time in 1969 were practically free of goitre (Gibson 1970). In 1971 I repeated my survey of trainee nurses aged 19-20 years at Royal Hobart Hospital. From 51, all of whom were born in Tasmania as in the previous survey, three very mildly enlarged thyroids were found. This is similar to the experience in non-goitrous areas.

Five years after iodation of bread, the goitre prevalence of preschool children and young adult females is similar to that reported for the middle-west of America by Brush and Altland, where prevalence of goitre in schoolchildren has fallen from 26 - 70 per cent to 1 - 4 per cent following iodine prophylaxis (Brush and Altland 1952).

However, at this time 24 hour excretion of iodine by many children in several areas was in excess of 200 mcg. and the reason for this was investigated. Results from this investigation are presented and discussed in Chapter 9.

CHAPTER 9

THE CHANGING IODINE ENVIRONMENT

TABLE 9 - 1URINE IODINE OUTPUT OVER 24 HOURS
IN MALES AND FEMALES IN FOUR DECADES

AGE GROUP (YEARS)	SEX	MEAN	IODINE
			(ug/24 HOUR) RANGE
20 - 29	M	246	94 - 348
	F	173	56 - 297
30 - 39	M	256	172 - 352
	F	210	103 - 359
40 - 49	M	264	193 - 381
	F	190	93 - 312
50 - 59	M	263	135 - 398
	F	228	118 - 371

INTRODUCTION

The increased iodine output by many schoolchildren prompted a further survey of the iodine excretion of people in other age groups. This is shown in Table 9 - 1.

Twenty-four hour collections of urine in the four age groups 20-29, 30-39, 40-49, 50-59 were made and the iodine content determined. These showed an excretion on average, much in excess to that expected from bread (Connolly 1971). Pittman and others in North America found urinary iodine excretion in 24 hours as high as 680 mcg. but as discussed in the previous chapter the concentration of iodine in bread in their region was high enough to account for this (Pittman 1969).

IODINE ADDED TO THE NATURAL ENVIRONMENT

The State of Tasmania is an island, separated from the mainland of Australia by Bass Strait which is over 200 miles wide. Transport between Tasmania and the mainland of Australia was limited until after the Second World War. Air services have been expanded considerably since then, bringing passengers and freight to all centres of the island. This freight includes foodstuffs grown elsewhere in Australia, from areas where soil iodine is in normal concentration. More foods of all types, both fresh and canned have been introduced since 1960 by several ships running on a regular schedule between Tasmania and other States. With increases in exports from Tasmania it can be assumed that foods low in iodine are con-

TABLE 9 - 2

SOME TASMANIAN FOOD IMPORTS
OVER THREE PERIODS OF TIME

TYPE	AMOUNT IN HUNDREDWEIGHTS		
	1948-49	1958-59	1968-69
MEAT	10,000	9,166	23,880
CHEESE	5,409	7,072	5,576
BISCUITS, CAKE	9,663	16,290	60,514

TABLE 9 - 3SOME TASMANIAN FOOD
IMPORTS FOR 1968-1969

TYPE	AMOUNT IN HUNDREDWEIGHT
MILK, CREAM (CONDENSED, DRIED)	31,308
VEGETABLES (FRESH, FROZEN, DRIED)	243,740
FRUIT (FRESH, PRESERVED)	13,494
FISH (FRESH, PRESERVED)	14,000

28

sumed overseas and in the other Australian States (Statistics of Tasmania, 1968-1969), but the Tasmanian contribution to these diets is small.

Table 9 - 2 shows imports from other States in the three periods 1948-49, 1958-59, and 1968-69, to illustrate the large and increasing amounts of some foods imported. The population has changed from 270,000 in 1949 to 388,000 in 1969 an increase of 40 per cent. Meat imports have increased by 140 per cent, biscuits and cake by 500 per cent.

Table 9 - 3 shows the large amount of other foods imported to Tasmania in the year 1968-69. From these imports, approximately 9 lb of meat, 12lb of milk, 25lb of biscuits, 30lb of fruit, 100lb of vegetables, and 5lb of fish produced in other States of Australia were consumed per head of population in 1968-69. Many other examples could be given of the increased consumption of food, not locally produced. Although iodized table salt is imported, it is not used extensively and contributes little to dietary iodine intake.

Thus by 1966, Tasmanians were known to be receiving an increase in iodine from imported foods, from bread, and a very small amount from salt. In addition, schoolchildren were receiving tablets of potassium iodide each week.

In addition it was discovered that a change had been made in the sanitizers used in the dairy industry. Hypochlorite-containing substances releasing chlorine had been replaced to a large extent by organic compounds releasing iodine. These substances, known

TABLE 9 - 4MILK IODINE ANALYSES SHOWING
EFFECT OF IODOPHOR SANITIZING

SOURCE	IODOPHOR USED	IODINE CONCENTRATION (mcg / 100 ml)
HOBART	YES	12.1 - 15.3
DEVONPORT	YES	15.7 - 20.2
BURNIE	YES	11.3 - 18.5
LAUNCESTON	YES	32 - 34.6
BOAT HARBOUR	YES	16.4 - 100
YOLLA	YES	70 - > 100
SPREYTON	NO	1.3
SCOTTSDALE	NO	1.6
DERBY	NO	2.3
SORELL	NO	1.7
MELBOURNE (VICTORIA)	YES	14

TABLE 9 - 5

EFFECT OF ORAL IODOPHOR IN
MILK ON 4 AND 24 HOUR UPTAKES
OF RADIOIODINE BY THE THYROID

FIG 9-5

EFFECT OF IODOPHOR IN MILK

<u>% Uptake ^{131}I</u>		<u>% Uptake ^{131}I</u>		<u>Urine Iodine</u>	
4 hr.	24 hr.	4 hr.	24 hr.	24 hr.	
9	20.5	4	11	1.2	mgm.
52.5	67	21	47	1.5	mgm.
20	34	6	12	2.6	mgm. *
17	36	7	3	1.5	mgm.
13	-	5	-	1.5	mgm.
-	30	-	5	7.75	mgm.

* Theatre Sister ? Iodine contamination

TABLE 9 - 6IODINE CONCENTRATIONS IN MILK PRODUCTS
CONTAMINATED WITH IODOPHORS

PRODUCT	IODINE CONCENTRATION (mcg / Kg)
MILK POWDER	654
MILK CHOCOLATE	436
CHEESE	782
ICE CREAM	396
CONCENTRATED MILK BISCUIT	1000

collectively as iodophors, were found to be more effective and easier to use (Twomey 1968, Elsley 1971). The iodophors are used to sterilize milking machines, storage vats, bulk milk tankers and processing plants. They contain up to 2 per cent of iodine. The concentrations of iodine in samples of milk from various areas are shown in Table 9 - 4 (Connolly 1971).

There is an obvious difference in the iodine content of milk where iodophors were used and milk from other areas. The wide variation in iodine concentration where iodophors were used was caused by very crude measuring methods for sanitizers in dairy farming, and the varying number of containers through which the milk passed to the factory. The effect of iodophor given in milk in a measured dose is shown in Table 9 - 5. 2 mgm. of iodine were given to seven subjects and 8 mgm. to the last. The radio-iodine uptakes before and after are shown in left and right columns respectively. The depression of uptake is seen. Urinary iodine estimation shows that the iodine is absorbed and excreted in the following 24 hour period. Not only has milk become a significant source of iodine, but some milk products contribute also. The iodine concentrations in cheese, ice cream, milk chocolate, milk powder and concentrated milk biscuit are shown in Table 9 - 6.

The manufacturing processes of these foods were investigated, in particular, ice cream. It was found that yet another source of iodine has been introduced, namely alginate. This substance is a high molecular

TABLE 9 - 7

ALGINATE-CONTAINING FOODS
CONSUMED IN LARGE QUANTITIES
IN TASMANIA

BAKERY FOODS	GENERAL FOODS	DAIRY PRODUCE
CAKE MIXES	CANDY	CHEESE SPREADS
DOUGH	CUSTARDS	CHOCOLATE MIX
ICINGS	DRESSINGS	CREAM
JELLIES	PUDDINGS	ICE CREAM
MERINGUES	SAUSAGES	WATER ICE
MACARONI	TOPPINGS	
PIE FILLINGS	CORDIALS	
SYRUPS	SOFT DRINKS	

weight polysaccharide produced from brown seaweed. It belongs to the class of "gums". Analyses of several samples of alginate were made, and concentrations of iodine of up to 9 mg/Kg were found.

Alginate has been used in food preparation throughout the world for many years, and its use is increasing. Inclusion of alginate in the Pure Food Regulations of each State of Australia was recommended by the Food Additives Committee of the National Health and Medical Research Council of Australia. The wide range of foodstuffs in which this substance is used is shown in Table 9 - 7. The use of alginate of high iodine content in the manufacture of ice cream, can produce up to 200 mcg. of iodine per gallon in addition to any amount derived from milk used in the manufacturing process.

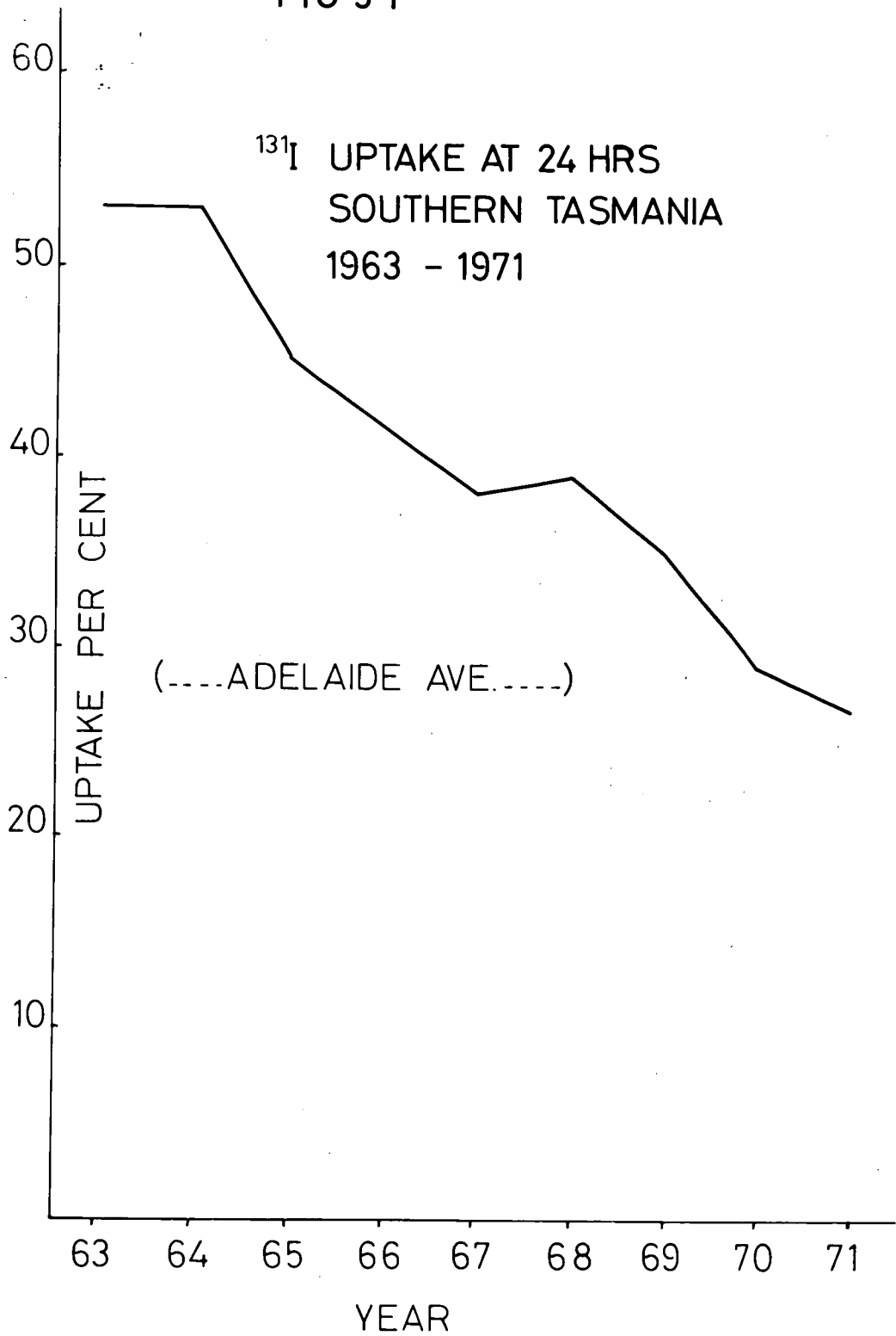
Iodophors are used widely as well as in the milk industry. The meat industry uses these substances in preparation and storage areas. An active chicken producing industry developed in Tasmania about 1963. The chickens are killed for the Tasmanian market in great numbers. The slaughterhouses use iodophors extensively as a wash and sanitizer. In many hospitals iodophors are used in "scrub up" procedures before surgery. A recent survey of urinary iodine excretion before and after using this material showed an average increased excretion of iodine of 70 mcg. per 24 hour period (Connolly 1972).

Evidence that the increase in environmental iodine is occurring progressively in other parts of

FIGURE 9 - 1

UPTAKE OF RADIOIODINE BY THE
THYROID AT 24 HOURS IN SOUTHERN
TASMANIA SINCE 1963 -- COMPARED
WITH THE NORMAL LEVEL IN
ADELAIDE, AUSTRALIA

FIG 9-1



the world is given by Hales (1972) from Sydney, Lamberg (1970) from Finland, and Pittman (1969) from America. Hales reports 24 hour urinary iodine outputs in 1961, 1966 and 1972 as 100 mcg., 150 mcg. and more than 200 mcg. respectively. Lamberg reports a change between 1959 and 1969 from 45-60 mcg. to 219 mcg. and Pittman reports many urinary iodines now greater than 600 mcg. in 24 hours.

CONCLUSION

Tasmania, which, by its isolation received little additional iodine in the past to correct a natural deficiency, has received extra iodine intentionally, mainly from the distribution of goitre tablets in the schools and iodated bread. By chance, imports and manufacturing processes have added further amounts of iodine. These additions are as follows

- (i) food imported from other Australian States;
- (ii) iodized salt; (iii) potassium iodide goitre tablets for school children; (iv) iodated bread;
- (v) "iodized" milk and milk products; (vi) "alginated" foods; (vii) iodophors used in industry and medicine; and (viii) iodine from miscellaneous sources such as cough mixtures, throat lozenges, skin preparations, thyroxine, anticholinergic drugs, anti-histamines and X-ray contrast media, etc.

The effect of this increasing iodine is shown in the progressive fall in the 24 hour uptake of radioiodine shown in Figure 9 - 1.

CHAPTER 10

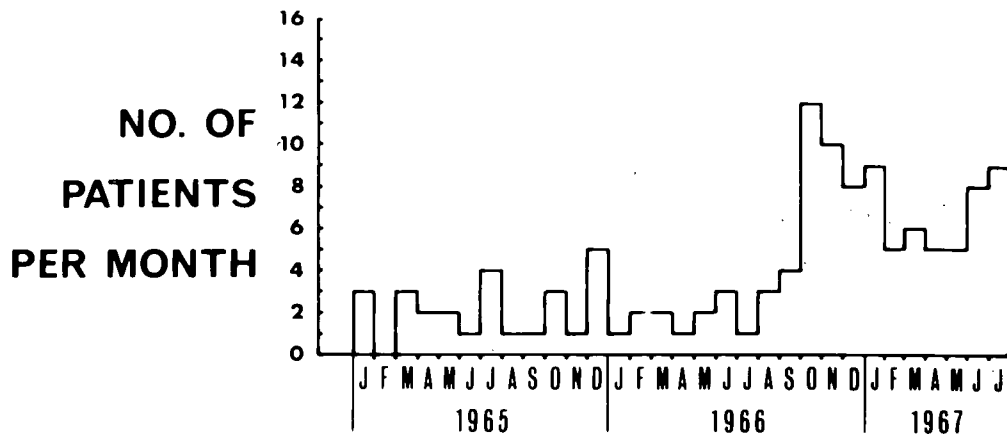
IODBASEDOW IN TASMANIA

FIGURE 10 - 1

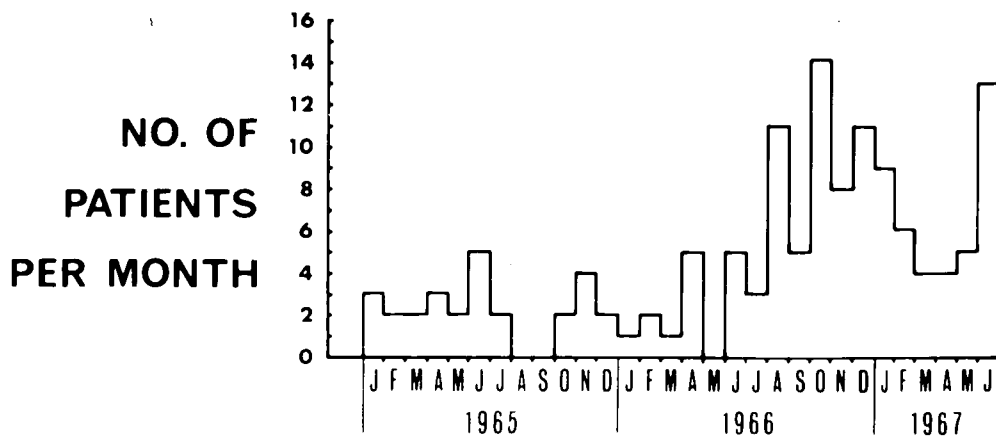
HOBART
MONTHLY INCIDENCE OF THYROTOXICOSIS

LAUNCESTON
MONTHLY INCIDENCE OF THYROTOXICOSIS

THYROTOXICOSIS . HOBART



THYROTOXICOSIS - LAUNCESTON



INTRODUCTION

Three months after the iodation of bread throughout the State in April 1966, an increased incidence of thyrotoxicosis was reported independently from the two main centres, Hobart and Launceston. The monthly incidence of the disease from these cities is shown in Figure 10 - 1.

Although a thyroid clinic was established at the Royal Hobart Hospital in 1948 with its own record system, criteria for diagnosis was unsatisfactory. In 1962 radioactive iodine (^{131}I) for the diagnosis of thyroid disease was introduced, and between then and 1965 I established the following criteria for the diagnosis of thyrotoxicosis in Southern Tasmania:

1. The clinical index of Crooks, Murray and Wayne (1959). A score above 22 was accepted as presumptive evidence to warrant further investigation

2. The uptake by the thyroid of an oral tracer dose of 5-10 microcuries of ^{131}I at 4 and 24 hours, using the technique described by Veall (1958). The normal range for these tests had to be changed progressively, falling as the iodine content of the environment increased (Figure 9 - 1)

3. The degree of saturation of thyroxine binding sites in plasma proteins as measured by the adsorption of triiodothyronine by resin originally and resin sponge later. The technique was that devised by Sterling (1961) modified in a "kit" by Abbott Laboratories. The accepted range was 85-118 per cent of pooled normal serum (T_3 resin)

4. Protein bound ^{131}I at 48 hours using the

PLATE 10 - 1

THYROTOXICOSIS RECORD
TASMANIA 1966 ---

THYROTOXICOSIS RECORD

DATE OF PRESENTATION _____ BREAD INTAKE _____ Oz. per week

ONSET OF SYMPTOMS _____ IODINE—
Modication _____

PREVIOUS GOITRE _____ Radiology _____

RESIDENCE _____ WATER SUPPLY _____

Glasgow Index	+	-	Date		
Dyspnoea on effort	1			T3 resin uptake/T.B.I.	
Palpitations	2				
Tiredness	2			PRI ¹³¹ I @ 48 hours	
Preference for heat		5			
Preference for cold	5			PBI (chemical)	
Indifference to temperature	0	0			
Excessive sweating	3			I ¹³¹ I uptake @ 4 hrs.	
Nervousness	2			@ 24 hrs.	
Appetite increased	3			@ 8 days	
Appetite decreased		3			
Weight increased		3			
Weight decreased	3			I ¹³¹ I uptake after T3	
Palpable thyroid—present	3			@ 4 hrs.	
absent		3		@ 24 hrs.	
Bruit over thyroid—present	2				
absent		2		24 hr. urine iodine	
Exophthalmos	2				
Lid retraction	2			LATS	
Lid Lag	1			Antibodies TRC	
Hyperkinetic movements—present	4			CF	
absent		2			
Fine finger tremor	1			PII	
Hands hot—present	2				
absent		2			
Hands moist—present	1				
absent		1			
Auricular fibrillation	4				
Regular pulse under 80		3			
80-90	0				
over 90	3				
				Therapy	
				¹³¹ I	
				Chemotherapy	
				Iodine	
				Surgery	
				Follow Up:	
				INDEX	
				HYPO	
				HYPER	
				EUTH	
				3/12	
				6/12	
				1 yr.	
				2 yr.	
				3 yr.	
				4 yr.	
				5 yr.	

Clinical Index

No. _____
Date _____

Recorded retrospectively on _____

Further clinical details overleaf.

24424

SURNAME

CHRISTIAN NAMES

DATE OF BIRTH

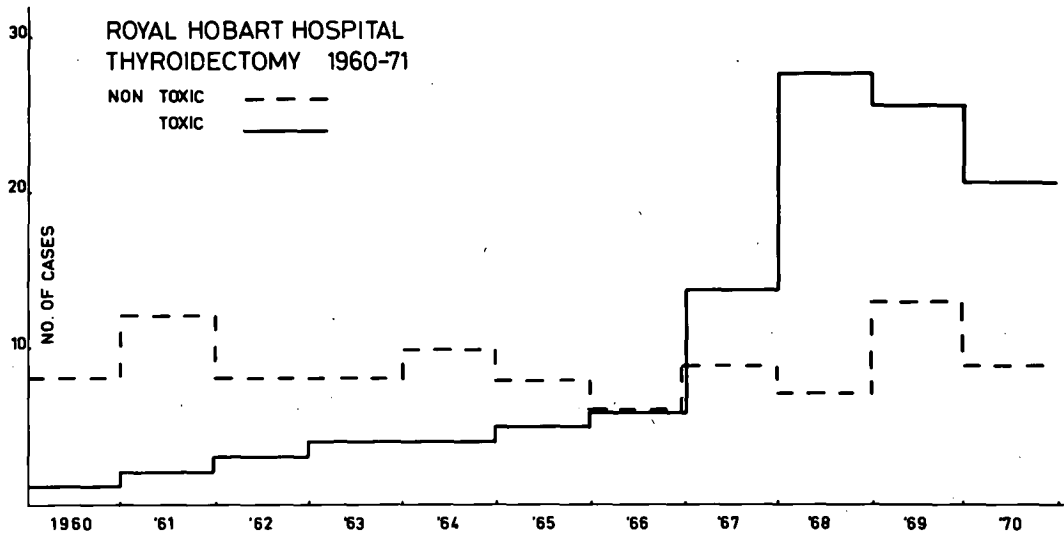
UNIT No.

O.P. No.

FIGURE 10 - 2

THYROIDECTOMIES
ROYAL HOBART HOSPITAL
1960 - 1970

FIG 10-2



technique of Veall (1958). The accepted normal range was from zero to 0.4 per cent of the administered dose of ^{131}I per litre of plasma

5. Protein bound ^{127}I (P.B.I.) was estimated for me by Laboratory Services Pty. Ltd., in Victoria, whose normal range using the acid ash technique is 3.5 - 7.5 mcg. per cent.

Later serum thyroxine estimations using competitive protein binding analysis devised by Murphey and Pattee (1964) again modified in a "kit" by Abbott Laboratories were used. This and other evidence was recorded on the protocol sheet shown on Plate 10 - 1. These facilities were available only at the Royal Hobart Hospital, serving approximately 200,000 people. Although some documentation of thyrotoxicosis was available before 1965 it was incomplete and not reliable. Hence cases occurring before this time are not included in the figures.

EVIDENCE FOR INCREASED INCIDENCE OF THYROTOXICOSIS

Other evidence for an increase in the disease is given in the Figures 10 - 2, 10 - 3 and 10 - 4. Figure 10 - 2 shows the number of thyroidectomies carried out at the Royal Hobart Hospital. It can be seen that subtotal thyroidectomy for cosmetic reasons, obstruction or suspicion of cancer remains at a steady rate, but surgery for thyrotoxicosis increased considerably in 1967. Although the numbers are small the figure suggests a gradual increase in thyroidectomies for thyrotoxicosis from 1960 before the sudden increase in 1967. Confirmation of the increased surgical rate is provided by Figure 10 - 3 showing a similar increase in the

FIGURE 10 - 3

CASES OF THYROTOXICOSIS RECEIVING
- RADIOIODINE THERAPY
SOUTHERN TASMANIA 1962 - 1970

FIGURE 10 - 4

CASES OF THYROTOXICOSIS PROVEN BY
RADIOIODINE DIAGNOSTIC TECHNIQUES
SOUTHERN TASMANIA 1962 - 1970

FIG 10-3

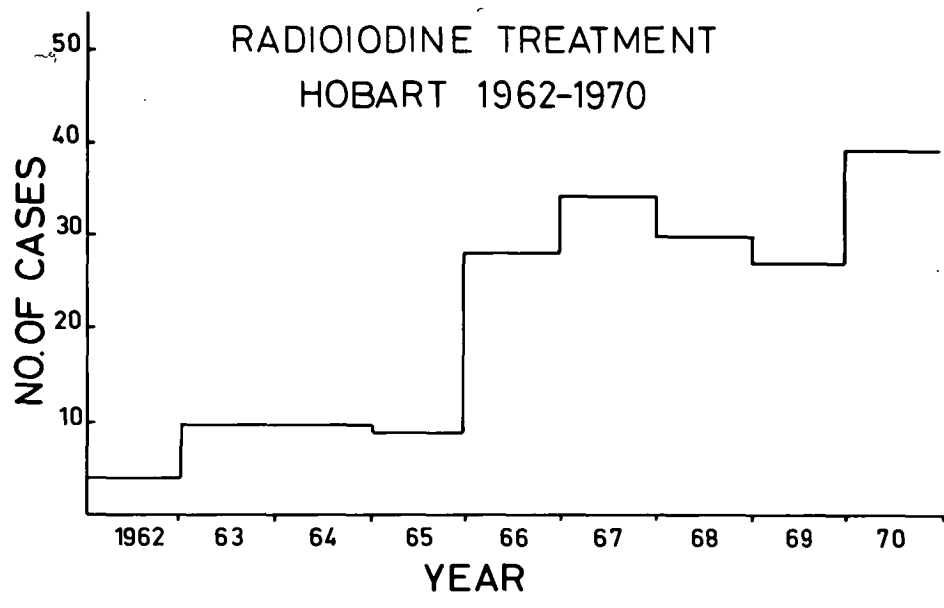
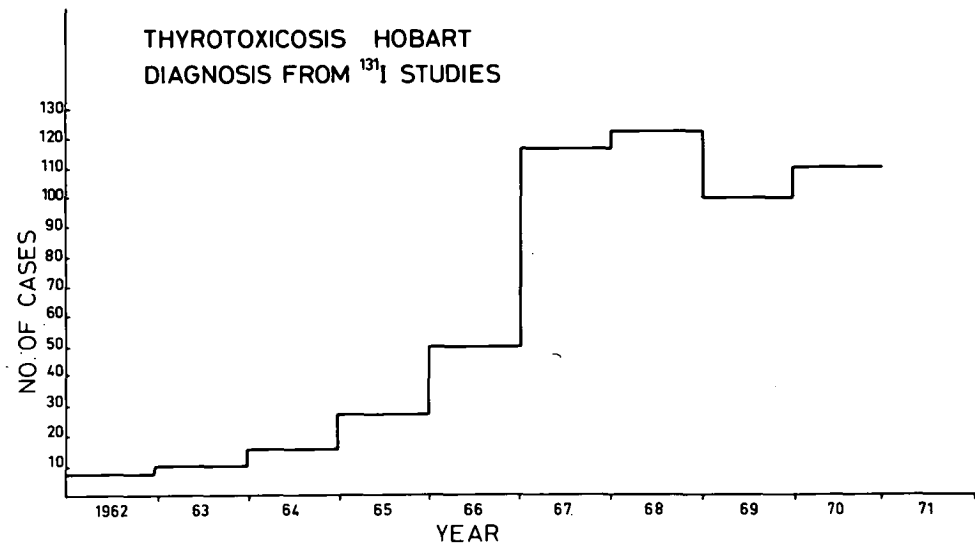


FIG 10-4



number of cases treated for thyrotoxicosis with radioiodine. Yet further confirmation is seen in the sudden increase in the rate of objective diagnoses provided by radioiodine studies (Figure 10 - 4). Note all increases occurred at the same time.

Carbimazole is distributed by one drug company in Australia. I was supplied with totals of the consumption of this drug for the State of Tasmania, at regular intervals since 1961. Whereas a gradual increase in consumption, found throughout Australia, was noted before 1967 the sudden large increase shown in Figure 10 - 5 was unique to Tasmania. The almost identical consumption for the North and South of the State is seen in Figure 10 - 6.

Investigations into possible variations in referral patterns to me over the years, differences in criteria for diagnosis before and after 1966, and the number of cases operated upon for thyrotoxicosis in private hospitals in Hobart were carried out. All of these factors were eventually ruled out as a cause for an apparent but spurious increase in the disease. In Table 10 - 1 the annual numbers of thyroidectomies for toxic and non-toxic goitre carried out at the Royal Hobart Hospital are compared with those for the three private hospitals in Hobart during the period 1966-71 inclusive. Both groups show a similar and sustained increase. Possible variation in diagnostic criteria was examined. Samples of cases were picked using tables of random numbers, comparing Clinical index, P.B.I., and T_3 resin. ^{131}I uptakes could not be compared since additional iodine intake meant the normally

FIGURE 10 - 5

QUARTERLY CONSUMPTION OF
CARBIMAZOLE
TASMANIA 1961 - 1971

FIG 10-5

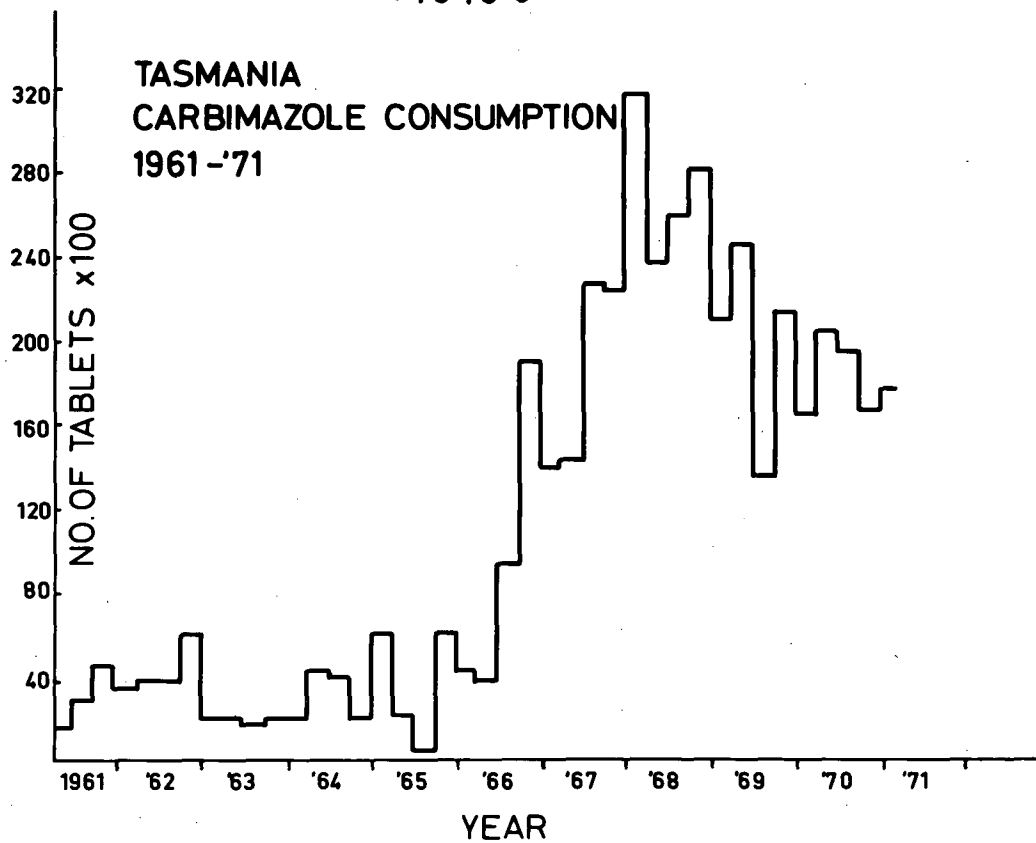


FIGURE 10 - 6

ANNUAL CONSUMPTION OF
CARBIMAZOLE
1963 - 1967

HOBART _____
LAUNCESTON-----

FIG 10-6

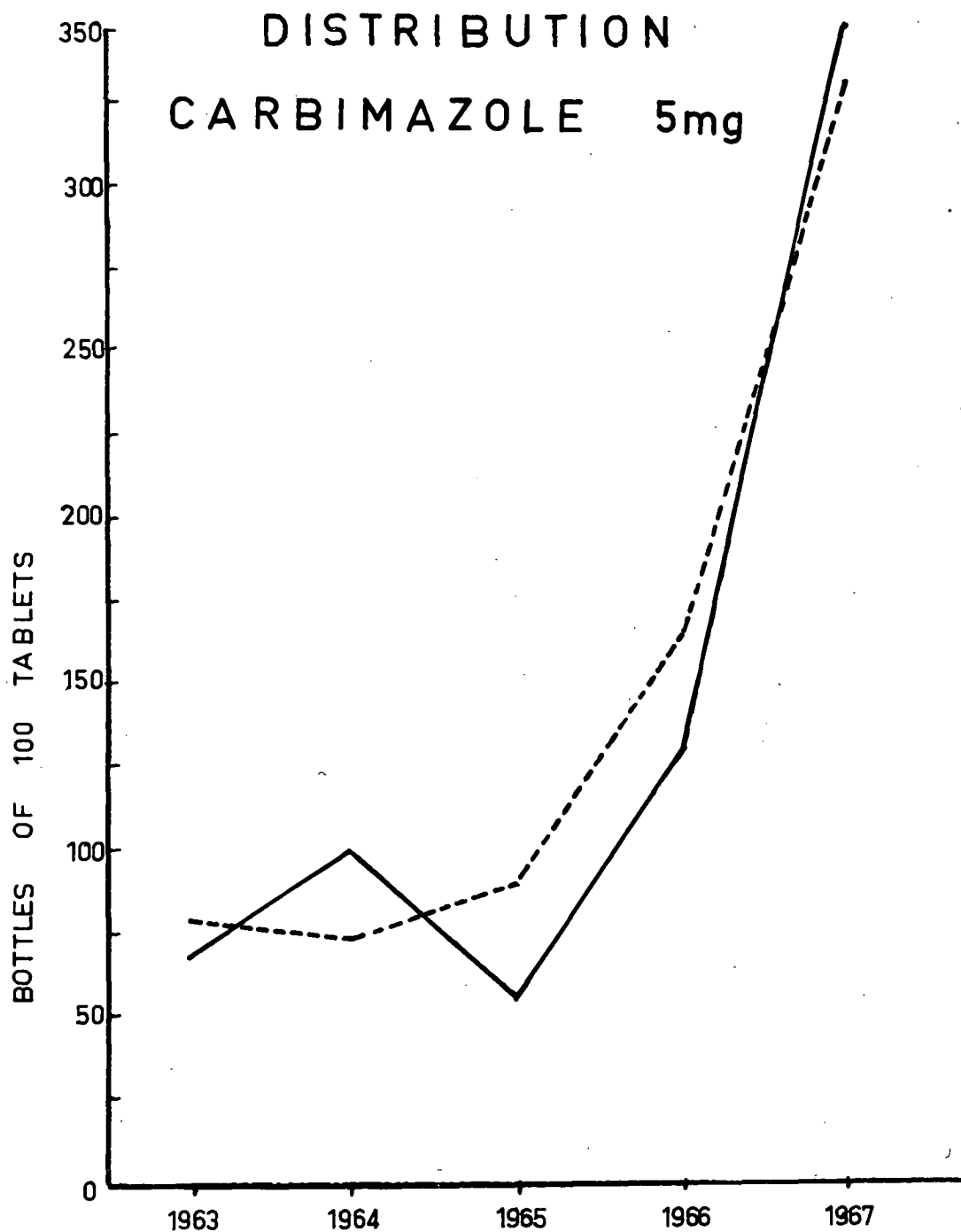


TABLE 10 - 1

THYROIDECTOMIES AT ROYAL HOBART
HOSPITAL AND PRIVATE HOSPITALS IN
SOUTHERN TASMANIA

YEAR	PUBLIC HOSPITAL	A	PRIVATE B	HOSPITALS C	TOTAL
1966	14	15	N.A.*	-	15*
1967	21	18	7	-	25
1968	36	27	15	1	43
1969	37	24	15	1	40
1970	30	16	N.A.*	1	17*
1971	22	18	17	1	36

* Figures not available from
one private hospital.

FIGURE 10 - 7

THYROTOXICOSIS SOUTHERN TASMANIA
RADIOIODINE UPTAKE AT 4 HOURS
1967 - 1968

FIG10-7

THYROTOXICOSIS

4 hr. uptake : 83 cases

30 June 1967 - 30 June 1968

average 59%

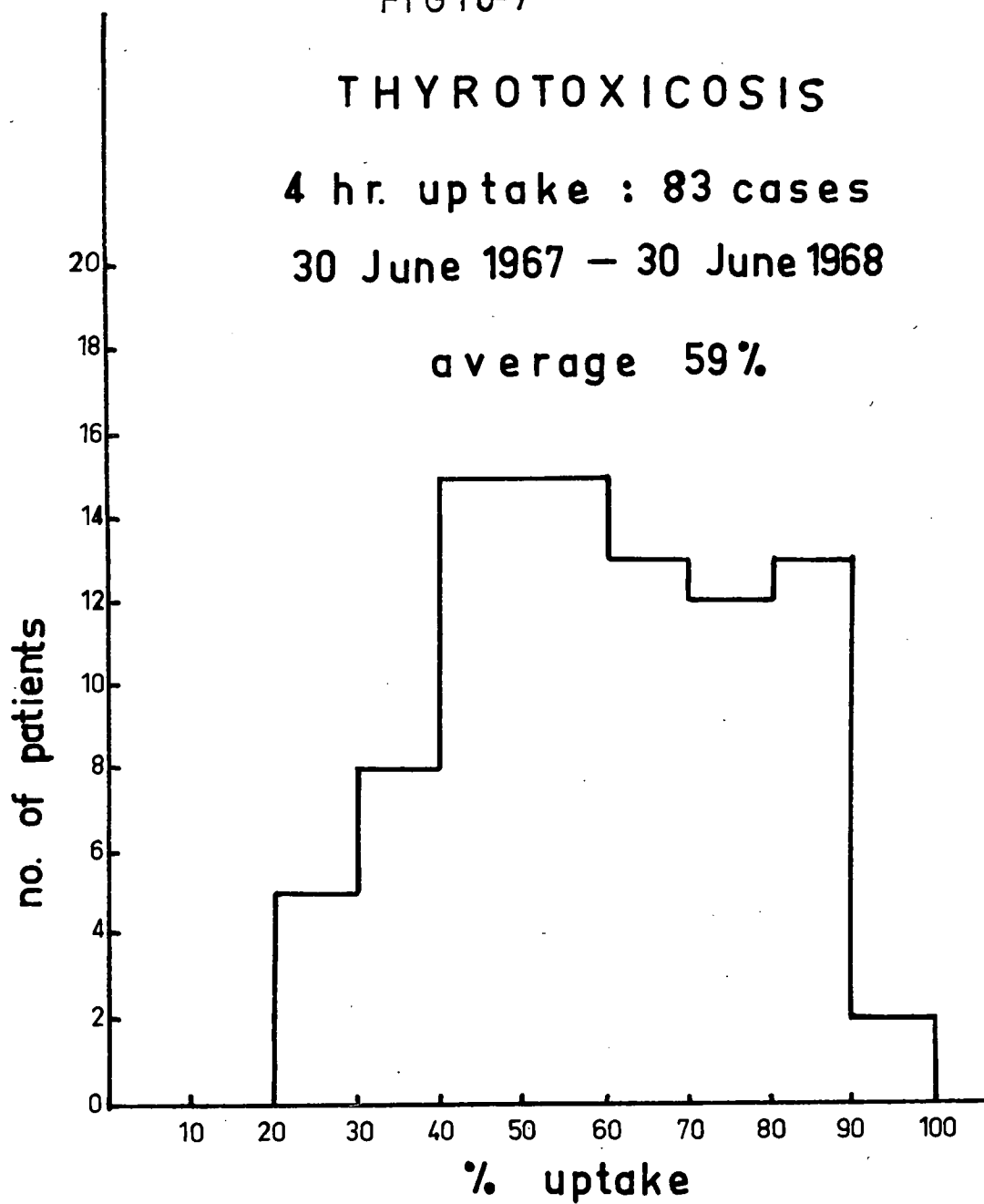


FIGURE 10 - 8

THYROTOXICOSIS SOUTHERN TASMANIA
RADIOIODINE UPTAKE AT 24 HOURS
1967 - 1968

FIGURE 10 - 9

INCIDENCE OF THYROTOXICOSIS
SOUTHERN TASMANIA 1965 - 1971

FIG 10-8

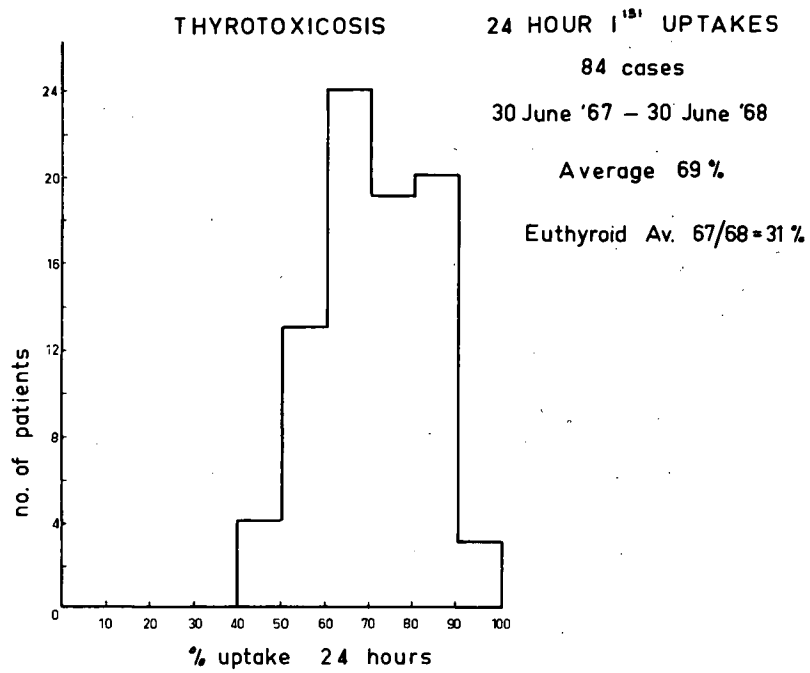


FIG 10-9

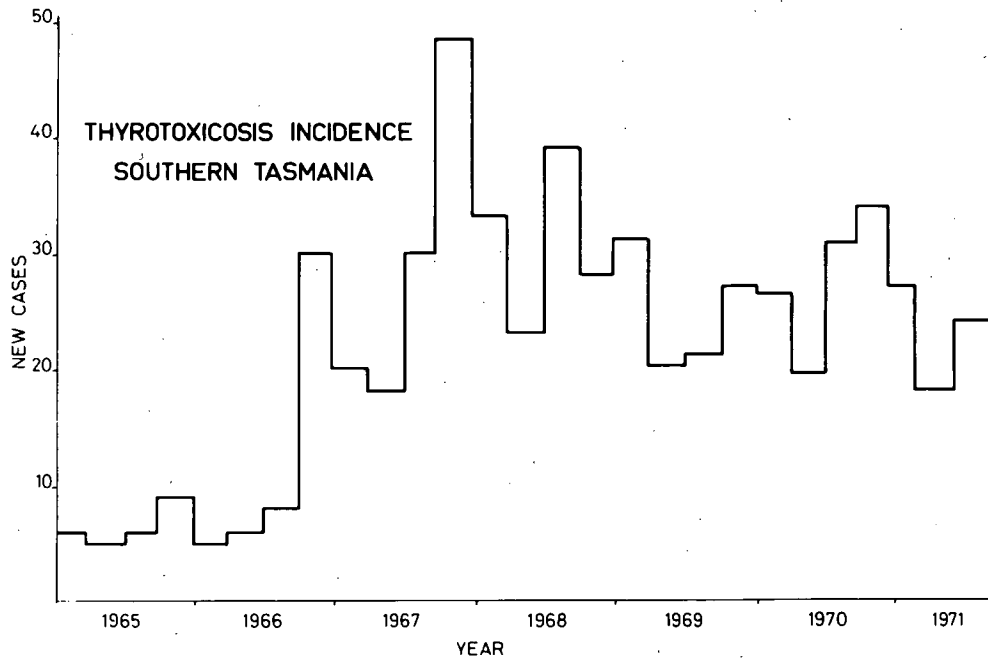


FIGURE 10 - 10

THYROTOXICOSIS SOUTHERN TASMANIA
AGE DISTRIBUTION

FIG 10-10

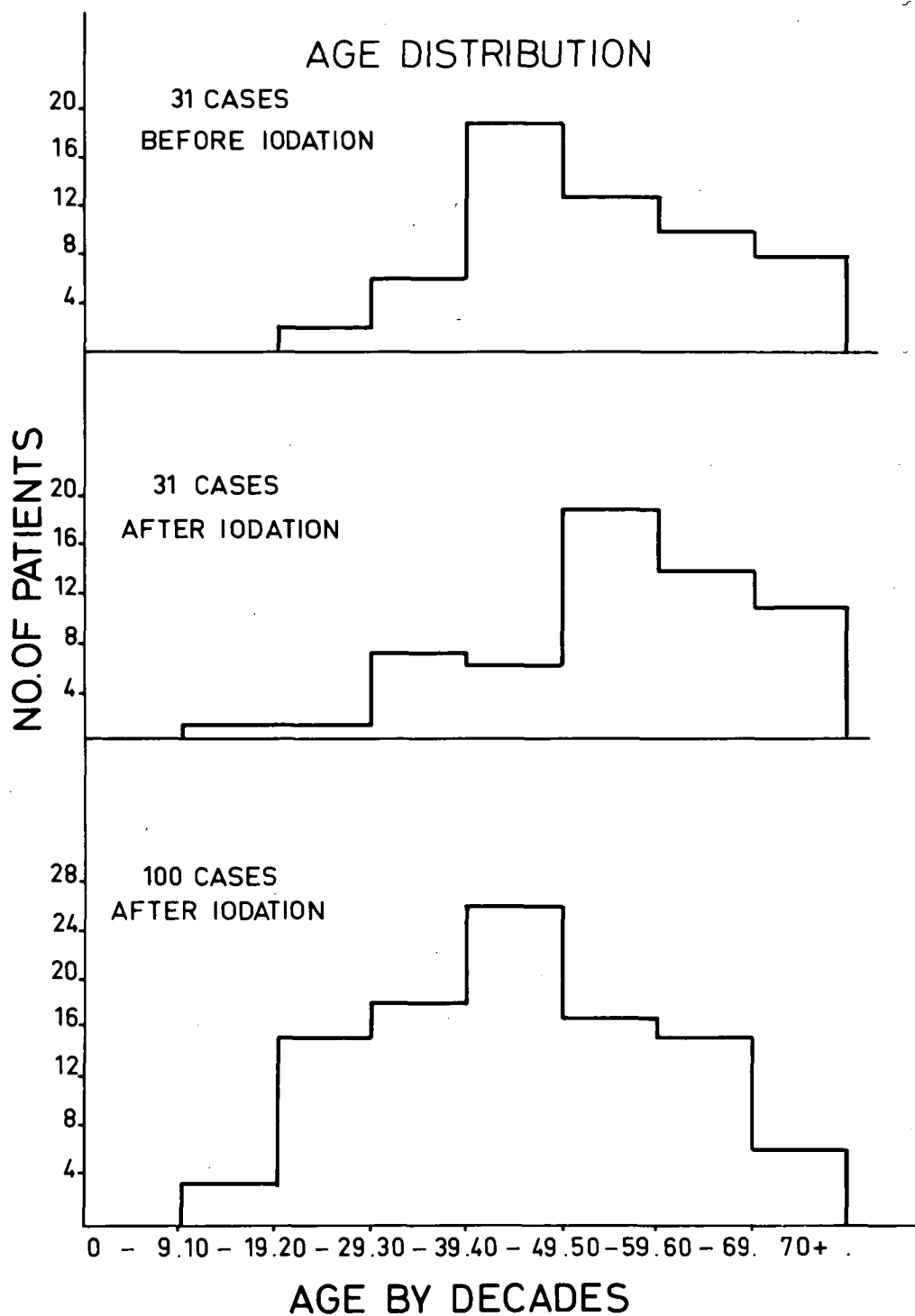


FIGURE 10 - 11

THYROTOXICOSIS SOUTHERN TASMANIA
AGE SPECIFIC INCIDENCES
1965 - 1971

Fig 10- 11

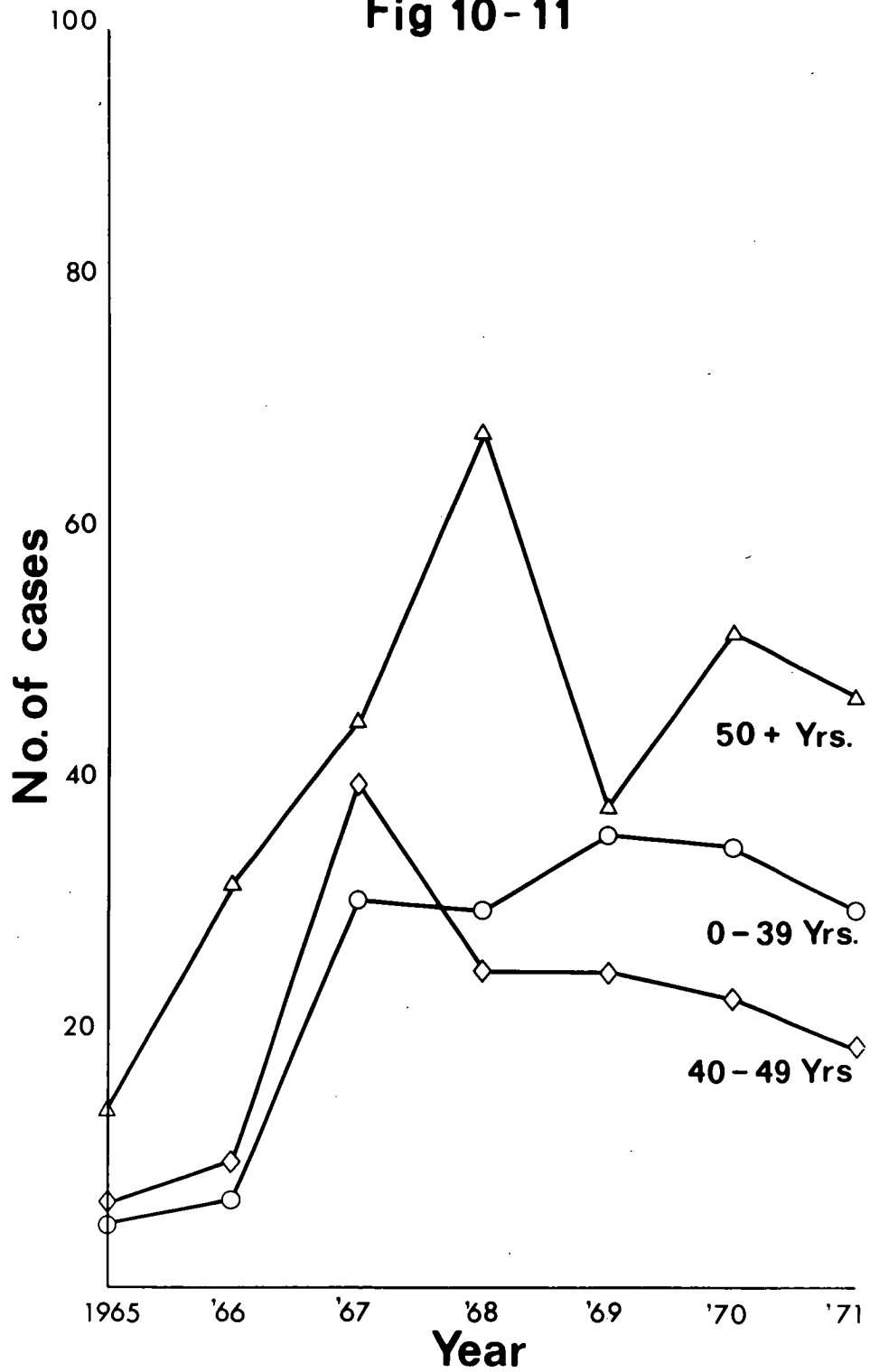
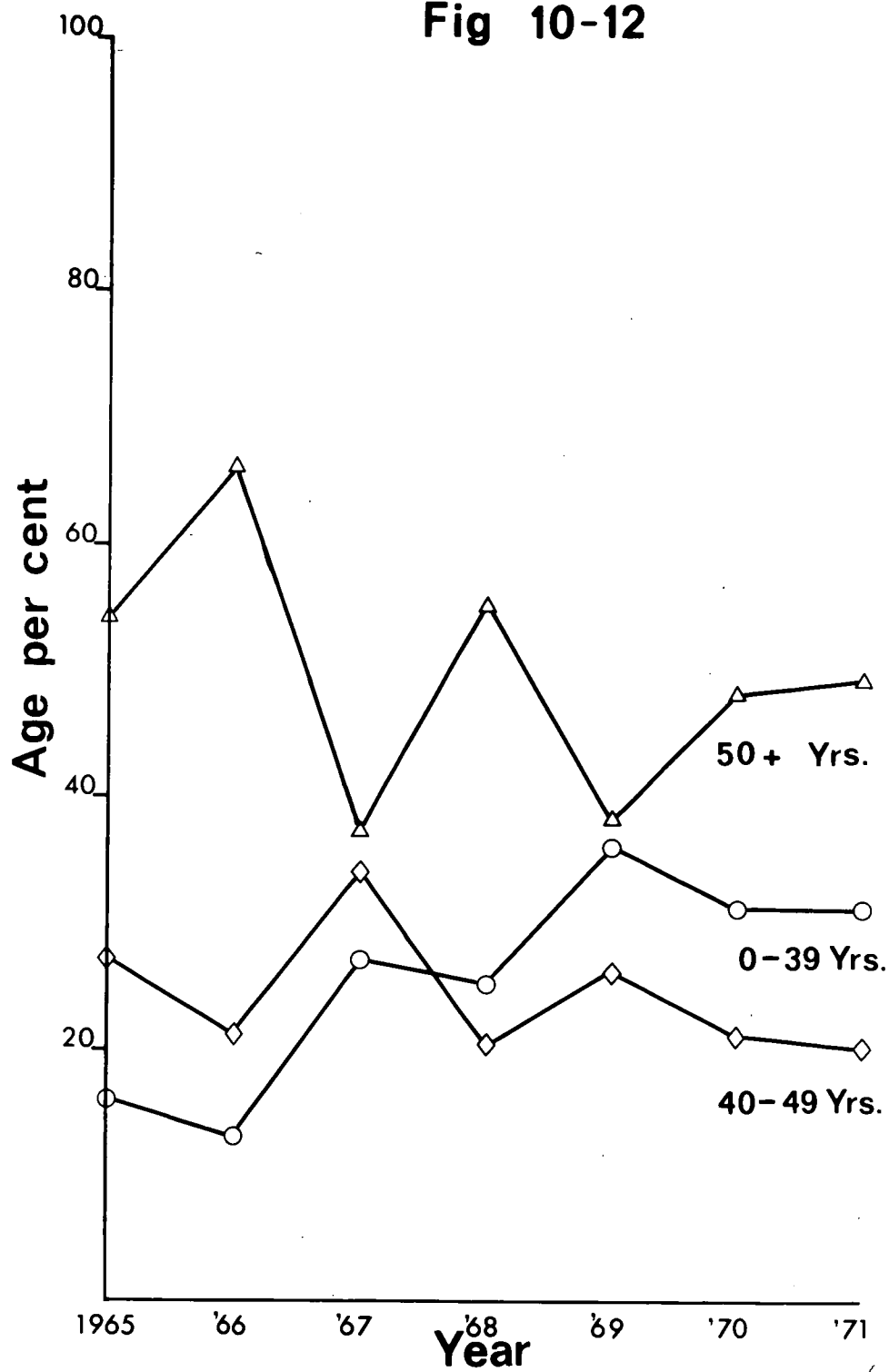


FIGURE 10 - 12

THYROTOXICOSIS SOUTHERN TASMANIA

PERCENTAGE OF AGE GROUPS RELATED
TO THE TOTAL ANNUAL INCIDENCE
1965 - 1971

Fig 10-12



accepted ranges had to be progressively lowered (Figure 9 - 1) and the wide scatter found in these tests (Figures 10 - 7 and 10 - 8) make comparison impossible.

The quarterly incidence of diagnosed thyrotoxicosis shown in Figure 10 - 9 was arrived at by the methods described above where a slightly increasing rate in 1965 and the first three quarters of 1966, was followed by an increase with a peak in 1967, and a continuing rate approximately three times that of 1965.

Changes in the age and sex of those affected have been suggested for Northern Tasmania (Stewart, Vidor and Hetzel, 1971) and this was thought to be so for the whole of the State (Connolly 1970). Figure 10 - 10 suggests that with larger numbers the difference is not significant. Indeed Figure 10 - 10 suggests that the age group affected may contain a larger number of younger people in the period after iodation of bread in 1966. Closer analysis of the age groups affected in the years 1965 to 1971 is shown in Figures 10 - 11 and 10 - 12 and in Table 10 - 3. In Figure 10 - 11 the greater increase in cases from the "50+" age group in 1966 is seen. In the 1967-68 period, although the younger age groups affected were increased, the oldest group continued to contain the larger numbers. This occurred during the peak incidence years shown in Figure 10 - 9. Since then the two older age group incidences have fallen but that for the younger one has remained at a steady elevated level relative to the 1965 period. Figure 10 -

FIGURE 10 - 13

THYROTOXICOSIS SOUTHERN TASMANIA

SEX DISTRIBUTION
INCIDENCE OF EXOPHTHALMOS

FIG 10-13

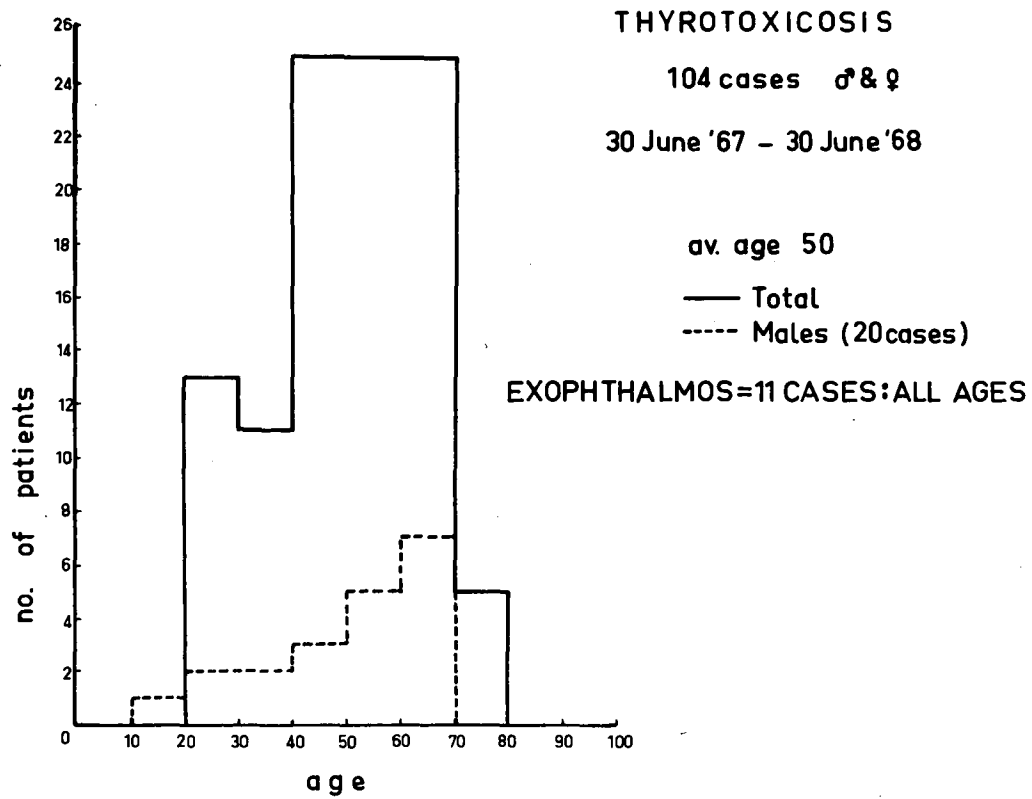


TABLE 10 - 2

THYROTOXICOSIS SOUTHERN TASMANIA

		1965	1966	1967	1968	1969	1970	1971
Monthly Incidence	J	3	1	9	16	10	4	10
	F	0	2	5	12	10	14	8
	M	3	2	6	5	11	8	9
	A	2	1	5	7	6	7	9
	M	2	2	5	10	7	9	5
	J	1	3	8	6	7	3	4
	J	4	1	9	14	6	13	9
	A	1	3	13	8	7	6	6
	S	1	4	8	17	8	12	9
	O	3	12	20	6	8	12	7
	N	1	10	16	13	10	11	8
	D	5	8	12	9	9	11	12
Annual Incidence		26	49	116	123	99	110	96

TABLE 10 - 3

THYROTOXICOSIS SOUTHERN TASMANIA

		1965	1966	1967	1968	1969	1970	1971
<u>Sex</u>								
	Males	6	10	16	23	19	22	21
	Females	20	39	100	100	80	88	75
	% Males	24	21	16	19	19	20	22
<u>Age</u>								
	0-39	5	7	31	30	36	35	30
	40-49	7	10	40	25	25	23	19
	50+	14	32	45	68	38	52	47
<u>Age%</u>								
	0-39	19	13	27	25	36	31	31
	40-49	27	21	34	20	26	21	20
	50+	54	66	39	55	38	48	49
<u>Exophthalmos %</u>		5*	6*	7	6	6	6	2
<u>Previous Goitre %</u>		80	80	81	81	76	77	75
<u>Born Tasmania %</u>		No enquiry		85	85	84	75	87

* Exophthalmometer not available

12 shows these trends more clearly, the three age groups being graphed as percentages of the total number of cases recorded annually. Thus, an increase in the incidence of thyrotoxicosis affected all age groups but the peak incidence of 1967-68 was produced mainly by the oldest age group. Since then the incidence of the disease in this and also the 40-49 year age group has fallen steadily. In contrast the incidence in the younger group has remained at a steady state. In Southern Tasmania no increase in the proportion of males affected has occurred, the percentage remaining at 20 approximately, throughout the period of observation (Figure 10 - 11). Exophthalmos as determined by an "Oculus" ophthalmometer has been seen in approximately 5 per cent of the cases only though mild lid retraction and lid lag were common. The cornea was at 18 mm or less, this figure being the average normal for the instrument.

The presence of preexisting goitre was given in the history in more than 70 per cent of the cases and in those who were uncertain, multinodular goitre was found on examination in almost every case. Over 85 per cent of the cases were born and had lived all of their lives in Tasmania, most of them being the second or third generation. The vast majority of their ancestors came from Great Britain and Eire. It is interesting that patients born on the continent of Europe, came from goitrous areas in Holland, Finland, Poland and Southern Germany, but the numbers were few. The monthly and annual incidences, sex ratios, age distribution, presence of exophthalmos and preexisting

goitre, and whether the patients were born in Tasmania are presented in Tables 10 - 2 and 10 - 3. All of these results confirm that a gradual increase in the incidence of thyrotoxicosis in Southern Tasmania was followed by a sudden increase in 1966 with a peak in 1967 and 1968. A continuing plateau at approximately four times the previous level forms the present pattern of this incidence. Similar results with minor variation have been found by workers in the Northern half of the State (Vidor 1972).

CHAPTER 11

DISCUSSION

INTRODUCTION

Some of the views previously quoted, in the chapters on the history of iodine and its effect on endemic goitre, are appropriate to the discussion of iodbasedow. De Quervain said that endemic goitre was the antagonist of true Basedow's or Graves disease, the incidence decreasing the closer one approached the centre of the endemic. On the other hand, he said that iodbasedow or iodine induced thyrotoxicosis occurred in areas of high endemicity but the number of goitrous people affected were few. It seemed to him that the lowest daily dose of iodine required for thyrotoxicosis to occur, was between a half and one milligram, and once established the disease could continue for months if not years. Jackson reported cases which supported this statement. In the latter half of the 19th century, it was remarked that large doses of iodide did not produce any adverse effect on syphilitics in Berlin, where goitre was not endemic but did do so in Switzerland. Matovinovic and Ramalingaswami suggested that a small proportion of people may be predisposed to iodbasedow, but could give no figures to support their statement.

The size of the dose of iodine, particularly the large amount given by Fyfe, Prout, Coindet and Rilliet, was thought to be of great significance. The reaction against iodine for the treatment of goitre which began in Coindet's time and remained throughout the 19th century was supported by Kocher who coined the name iodbasedow in 1910. The first attempt at goitre

prophylaxis in Haute Savoie in 1919 appeared to support these views. Large doses were used, many cases of thyrotoxicosis occurred, and the programme was stopped because of this complication.

Marine, Lenhart and Kimball gave small intermittent doses of iodide to 5,000 children with good effect without any cases of thyrotoxicosis developing. Encouraged by this and the excellent response of patients to iodine before thyroidectomy, introduced by Plummer, the substance was used in the treatment of goitre in the U.S.A., particularly in areas of endemic goitre. Large continuous dosage of iodide in tablet or liquid form was used by many physicians in these regions. This was followed by an increased incidence of thyrotoxicosis reported by Jackson, Plummer, McClure, Clute, Mason, Dinsmore and Boothby in the years 1920-1935. Means and Lerman, working in a non-endemic goitre area, denied that such a condition could exist, but later modified this view. One may deduce from these observations that small intermittent dosage in young people, even in an endemic goitre region, would be free from the risk of inducing thyrotoxicosis, but this may not apply to all adults in such areas receiving continuous iodine therapy.

In recent years even the existence of iodbasedow was doubted by most world authorities, because of lack of any convincing documentation. Thus Matovinovic and Kovacic reported one case of thyrotoxicosis which occurred when 1,000 goitrous adults were given 5-15 mgm of potassium iodide daily. Stanbury reported one case

from Mendoza after a daily dose of 1.5 mgm of potassium iodide was given for several weeks. Ibbertson from the Himalayas, Buttfield, Hetzel and Choufoer from New Guinea, Stanbury and Scrimshaw from South America reported no cases after single intramuscular depot injections of iodised oil in goitrous people. Clements, discussing iodide prophylaxis for endemic goitre, stated that the opinion of all authorities was that iodobasedow was not a risk if iodised salt was made mandatory in any country (Clements 1954). Marine, in 1954, recognising the risk of inducing thyrotoxicosis in endemic goitre regions, and believing it was dose dependent, recommended a conservative concentration viz. iodide 1 in 100,000. This view was shared by Hercus in New Zealand, Astwood and Greer in U.S.A. and Richard in Switzerland.

The daily requirement of iodide is given by various workers at about 100 mcg., and Koutras has said that amounts up to 500 mcg. daily could be taken without risk. Some doubt has developed about the daily amount of iodine required to induce thyrotoxicosis in some goitrous people, in endemic areas. Van Leeuwen showed that a daily intake of 100 mcg. of iodine from bread produced thyrotoxicosis without exophthalmos in some goitrous people. Ek and others reported toxicity following the iodine repletion test of Fraser. Some cases of thyrotoxicosis followed single exposures to iodide according to Laroche and Hirsch.

Thus all shades of opinion exist at the present time:

1. Iodbasedow does not exist as a disease entity.
2. Iodbasedow is induced by large doses of iodine in some adults with endemic goitre.
3. Iodbasedow will not occur in these adults if the daily dose of iodine is kept below 500 mcg.
4. Iodbasedow will occur in some susceptible adults with endemic goitre even with a daily intake of 100-200 mcg. which is the normal requirement.

TASMANIA AFTER 1966

Excretion of urinary iodine, in the people of Tasmania, has risen from a mean of 50 mcg. in 1966 to about 200 mcg. daily at present. These levels of excretion, plasma inorganic iodine (Hetzel 1968), radioactive iodine uptake studies, and protein bound iodine which have been measured in a large number of people show that excess iodine has not been consumed. Iodine deficiency in the natural environment has been shown, in preceding chapters, to be present in Tasmania. The goitre surveys by Clements in 1949 and urinary iodine excretion at that time proved that the State was an area of endemic goitre due to moderate iodine deficiency. There is no evidence to support the presence of goitrogens acting in Tasmania at any time. The type of goitre, thyrotoxicosis, thyroiditis and cancer, occurring in this environment, were described in Chapter 6. In Chapter 8 the changes in iodine nutrition due to imports, iodine in milk, alginates etc., before iodation of bread were discussed. A gradual increase in iodine consumption, by most of the people of Tasmania over the past twenty years has occurred.

Tasmania, a moderately iodine deficient endemic goitre region, producing multinodular goitre in its inhabitants, particularly females, introduced a method of universal increase in iodine consumption through bread iodation in 1966. This was done because of the harmful effects of goitre. The World Health Organisation has stated in many publications that endemic goitre was a huge problem, because it was associated with increased incidences of cretinism, thyrotoxicosis, cancer and respiratory obstruction. Morbidity and mortality from thyroid disease, in areas of severe endemic goitre, were said to be very large and uneconomic, in the modern world. The prevention of the disease was simple, employing various methods of prophylaxis with iodine to suit local conditions. Areas of severe iodine deficiency, (New Guinea Highlands, Himalayas, Congo, Andes) were the main sources of information and concern.

The information available in Tasmania, presented in Chapter 7, suggests that neither cancer nor thyrotoxicosis is more common here than in other parts of the world. In the same chapter any figures based on mortality rates were shown to be of little value, because of the poor quality of the death certificates. I have no exact figures for the prevalence of cretinism in Tasmania. Newman and Millar, who were the only specialists in this field from 1948 until the beginning of the University of Tasmania Clinical School in 1967, say that cretinism is always of the athyroidal type and is very rare. This has been my experience from my Department of Endocrinology, where

in vitro thyroid function tests of infants suspected of having this condition are carried out. Enquiry at Royal Derwent Hospital, the only mental institution in the State, revealed no cases of the gross but specific neuronal deficit of cretinism, with normal thyroid function, as described by Stanbury, Buttfield, Pharoah and Hetzel. This is not surprising as all cases described by these workers arise only in areas of severe iodine deficiency. "It may be said in summary that endemic cretinism is the most important aspect of endemic goiter. It occurs only in association with severe endemic goiter and is correlated with the severity of the endemic. It has been assumed that it arises because of foetal deprivation of thyroid hormone during critical phases of development but this hypothesis lacks proof at present" (Stanbury 1970). Evidence available from Southern Tasmania suggests that the degree of iodine deficiency associated with endemic goitre in this State is insufficient to produce the cretinism discussed by Stanbury. It may be relevant that before 1960 when iodine in the environment had not been sufficiently enriched, protein bound iodine levels were not below the normal range. This is in contrast to findings by Buttfield, Hetzel and others from areas where severe iodine deficiency and endemic cretinism occurs. The rare cases of cretinism seen in Tasmania consist of severe mental deficiency and hypothyroidism due to agenesis of the thyroid gland.

Radiological evidence of tracheal obstruction by thyroid enlargement, particularly if retrosternal,

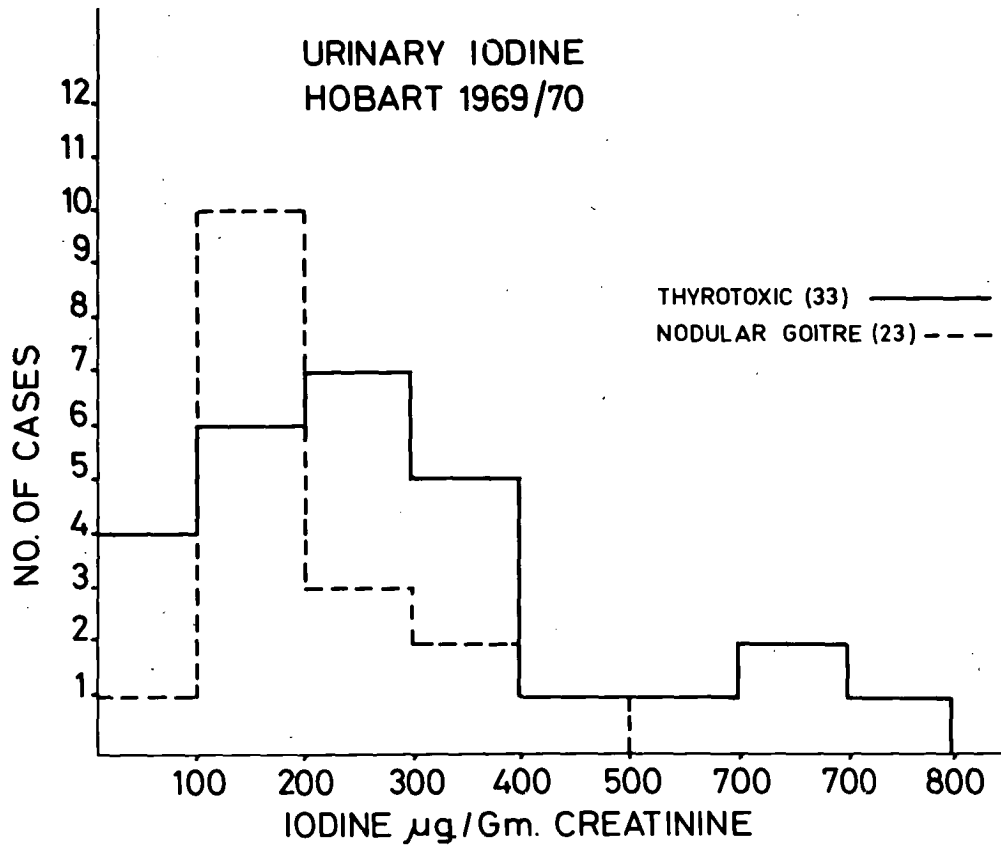
is commonly found but evidence of respiratory obstruction is uncommon, forced expiratory ventilation tests being normal for age. Abnormality in most cases, is accounted for by lower respiratory tract pathology. However, cases have presented, with clear cut evidence of chronic obstruction, which has been relieved by surgery. With no evidence for an increased incidence of thyrotoxicosis in Tasmania before 1966, no evidence for an overall increase in cancer or cretinism and with very few cases of tracheal obstruction from retrosternal goitre, prophylaxis with iodine could be questioned. Iodine induced thyrotoxicosis with morbidity and at least some mortality is weighted against the cosmetic effect in middle aged females.

The actual incidences of thyrotoxicosis and cancer may not be different from those in non endemic areas as shown in Chapter 7, and indeed for the former may be less. Papillary cancer which is unrelated to endemic goitre has an excellent prognosis as discussed previously. The opposite applies to the very malignant thyroid lesions occurring in later life. Therefore, the removal of endemic goitre with prophylactic iodine lowers the incidence of this latter condition. Similarly, the later age of onset of thyrotoxicosis, shown in Southern Tasmania before and for two to three years after iodation of bread, corresponds to the age of toxic nodular goitre in Switzerland, cases of primary Graves' disease being very uncommon. This is the experience of all surgeons in Hobart and is supported by the findings of the 500 sections which were reviewed in Chapter 6. It may be argued that iodine deficiency protects people in youth from Graves' disease, post-

FIGURE 11 - 1

URINARY	IODINE	EXCRETION
TOXIC	NODULAR	GOITRE
NON-TOXIC	NODULAR	GOITRE

FIG 11-1



poning the condition until later in life in some and definitely in others. Toxic nodular goitre may occur as a natural event or following exposure to extra iodine. The important point is that thyrotoxicosis, though less florid clinically in older people, produces cardiac complications due to preexisting coronary atherosclerosis. Cardiac irregularity, principally auricular fibrillation, leading to congestive cardiac failure, is common in the elderly thyrotoxic and carries a high mortality rate if left untreated.

Reasons for iodine prophylaxis in Tasmania can be listed as follows:

1. Higher mortality rate from thyrotoxicosis in the elderly.
2. Higher mortality rate from cancer of thyroid.
3. Obstruction to the trachea.
4. Cosmetic reasons in females.

THE RESULT OF INCREASING IODINE IN THE ENVIRONMENT OF TASMANIA

There is no doubt that a slow increase in environmental iodine occurred before 1966 and contributed to the reduction in goitre prevalence even before iodation of bread. There is some evidence from the Figures 10-2, 10-3, 10-5, 10-10 that it was accompanied by a slight increase in thyrotoxicosis. The sudden increase in incidence of the disease followed the introduction of extra iodine, by design in bread and by chance in milk and milk products, raising the consumption of iodine to a normally acceptable range, as reflected in urinary iodine excretion (Figure 11 - 1). In this figure the excretion of iodine which is a direct measure

TABLE 11 - 1

ANNUAL INCIDENCE OF THYROTOXICOSIS
BEFORE AND AFTER IODINE IN
SOUTHERN TASMANIA

BEFORE 1966	25	or	1/8000 population
AFTER 1966	100	or	1/2000 population
DIFFERENCE	75	or	1/2800 population

of its consumption is seen to be in an acceptable range for both toxic and non-toxic goitrous people. Levels are lower than those reported for normal people in U.S.A. (Pittman, Sachs and others).

The age, sex, presence of nodular goitre, absence of eye signs and frequent association with congestive cardiac failure and auricular fibrillation, make up the picture of toxic nodular goitre of middle and old age. In Chapter 10 evidence was produced to suggest that in the early period following iodation of bread in Southern Tasmania the elderly were prone to develop thyrotoxicosis but the trend is now towards the younger age groups, where little change in incidence has occurred since the initial rise in 1967.

The experience of iodbasedow in Tasmania and its apparent absence in other parts of the world can be reconciled when one considers the following factors. It has been shown that the incidence of iodbasedow as seen in Tasmania occurs in people whose average age is 50 years, with a range of 40-70+. The expectation of life in the Himalayas, Andes, New Guinea Highlands and the Congo, is far less than this. The habit of primitive and emerging people to conceal sickness, the inability of the sick to travel by foot to the medical centres and the relatively crude methods of some investigators are several reasons for the failure to find these cases. I am not being over critical of the extremely well planned experiments by world authorities, but to miss the diagnosis of mild thyrocardiac disease, masked thyrotoxicosis as it is often called, in the jungles of the emerging countries is

understandable.

But the incidence of iodbasedow is more important than any other factor and puts the disease in its proper perspective. From Table 10 - 1 the annual incidence of thyrotoxicosis in Southern Tasmania is approximately 100, the population being about 200,000. Thus all thyrotoxicosis occurs at a rate of one case per 2,800 people per year. The annual incidence of thyrotoxicosis before frank iod-basedow developed was 25, as shown in Table 10 - 2. The average annual incidences before and after 1966 and their ratios to the population of Southern Tasmania are shown in Table 11 - 1.

The populations screened by Matovinovic and Kovacic, Ibbertson, Stanbury, Buttfield and Hetzel were too small to expect to find a significant increase. Any population below 50,000 would produce such a small increase, that it is likely to go unnoticed, if the ratio is similar in all parts of the world where endemic goitre exists. This may not necessarily be so, as the degree of iodine deficiency may increase the thyroid response qualitatively as well as quantitatively. The one report of three cases of iodbasedow in elderly goitrous females after intramuscular iodised oil was injected into 960 subjects by Fierro-Benitez and others in Ecuador, supports this latter hypothesis. The closed community in which these workers operated with almost complete supervision of the population is significant (Fierro-Benitez 1970). Conversely the degree of iodine deficiency may protect more people from thyrotoxicosis

in direct proportion to its severity and the introduction of iodine to such communities may produce more cases.

THE FUTURE IN TASMANIA

Iodbasedow has become established in Tasmania, but to say that this is due to iodine in normal amounts is too simple. No answers have been given to the questions: Why does it attack late middle aged females with nodular goitre? Why, in a community where goitre in this sex and age group is so common, does it attack so few? Why has it not continued to be recorded in U.S.A. where people with endemic goitre have been supplemented with larger amounts of iodine? Was it that the thyrotoxicosis incidence in that country rose in the years of prophylaxis before the Second World War and no further effect from iodine has occurred or will occur? Certainly there is evidence from the progressive lowering of radioiodine uptakes in many centres in U.S.A. that iodine repletion has occurred there (Oddie 1970).

Adams maintains that, in all communities, there are people who are immunologically fated and prone to develop thyrotoxicosis at some stage in their lives (Adams 1971). This state results from the inheritance by these people of an immunoglobulin, either long acting thyroid stimulator (L.A.T.S.) or L.A.T.S. protector, which prevents L.A.T.S. from being destroyed by body tissue (McKenzie 1961, Adams 1971, Chopra 1971). The process is a continuing one and is prevented or postponed by iodine deficiency as overt diabetes is prevented or postponed in those prone to

diabetes mellitus by carbohydrate deficiency. If this is so, the incidence of thyrotoxicosis will remain in Tasmania at one per 3000 indefinitely unless iodine deficiency returns.

Iodine deficiency, over the years, produces multinodular goitre, some showing autonomous nodules which have increased iodine uptake as described by Demeester-Mirkine and Ermans (Demeester-Mirkine 1967). They showed that temporary increase in iodine consumption, by such people, produced the signs, biochemically at least of thyrotoxicosis. If this were the reason for the iodbasedow phenomenon the reduction of nodular goitre over the years should result in a reduction of thyrotoxicosis. It has been found however, that the histopathology of thyrotoxicosis is sometimes found in parts of the gland between the well formed nodules. I have examples of both types as seen by thyroid scanning and histological examination of biopsy material.

Perhaps the inherited tendency to thyrotoxicosis requires a nodular goitre and iodine deficiency to produce frank iodbasedow. When iodine deficiency is overcome and nodular goitre disappears from the community iodbasedow may cease also. However, the removal of iodine deficiency in younger people may allow some circulating substance, inherited or acquired, to produce Graves' disease. This theory appears to best fit the present situation in Tasmania.

If this is so, the overall rate of thyrotoxicosis will not change but the age of affected people will become younger, approaching that seen in non-endemic areas.

FIGURE 11 - 2

THYROTOXICOSIS SOUTHERN TASMANIA
AGE SPECIFIC INCIDENCES
1965 - 1971

Fig 11-2

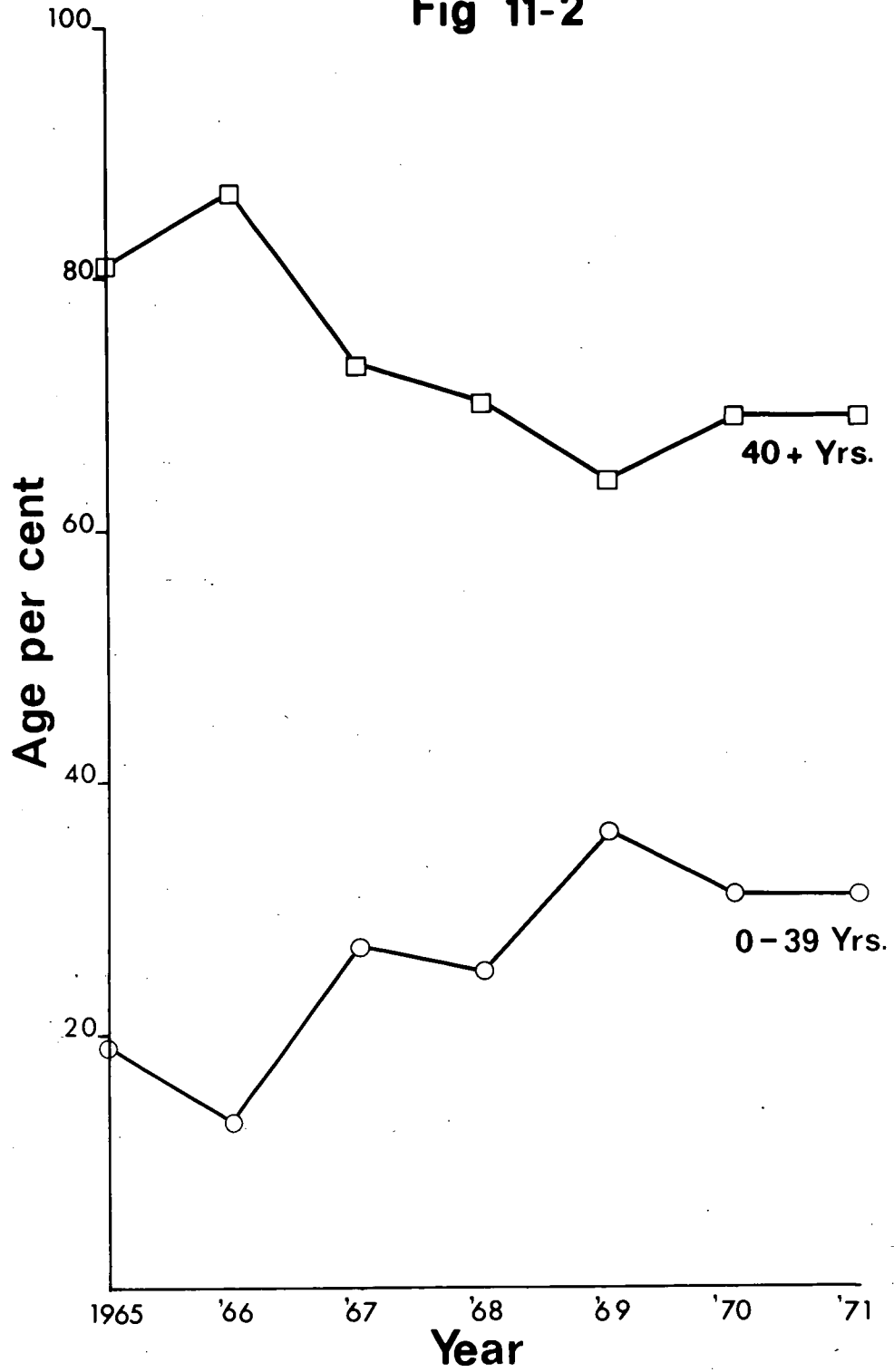
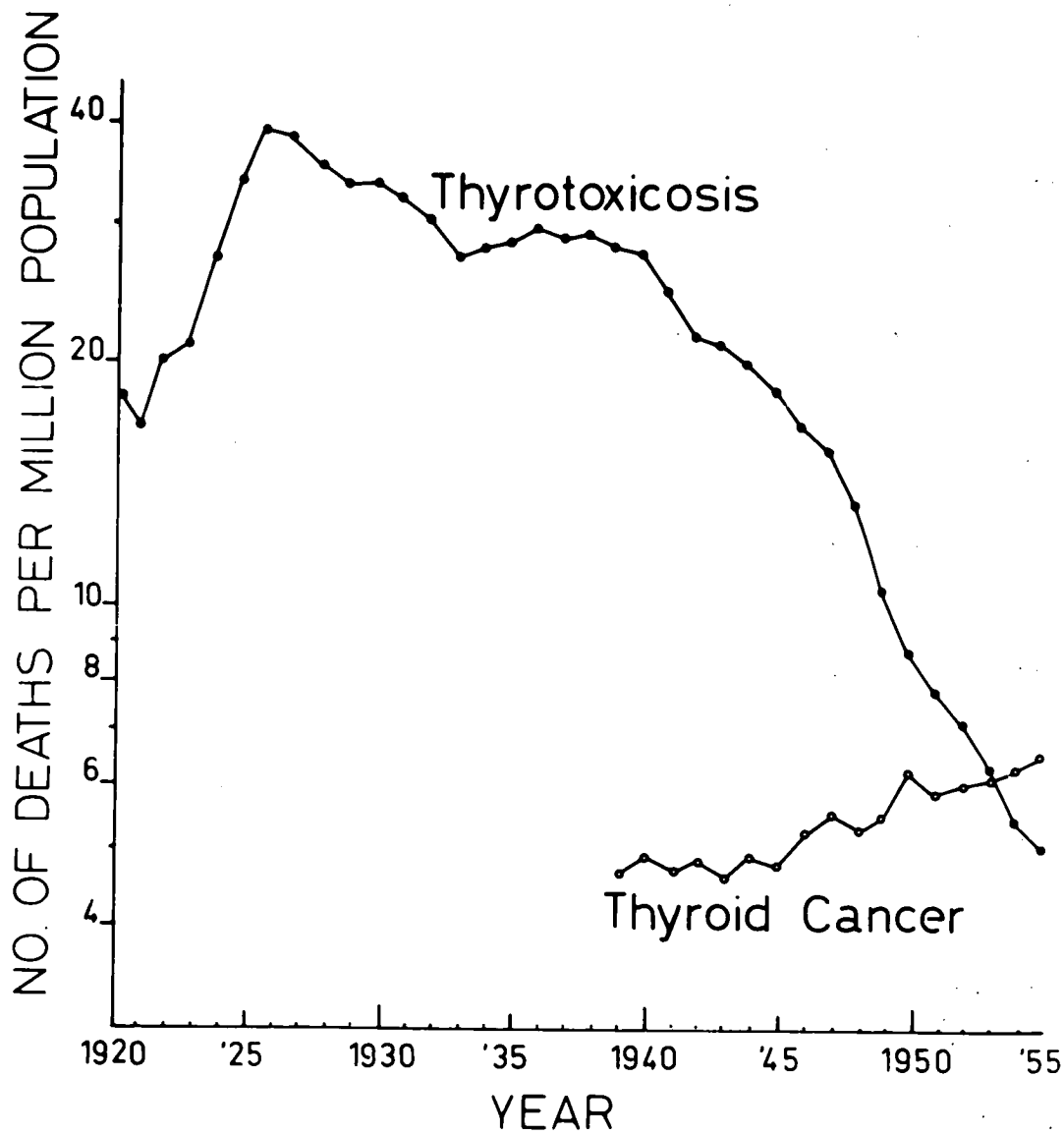


FIGURE 11 - 3

MORTALITY RATE FOR THYROTOXICOSIS
AND THYROID CANCER
U.S.A.
1920 - 1955



Support for such a view is given in Figure 11 - 2 where the percentage of thyrotoxic patient in the older age group is declining as the young age group increases. It is too early to make a definite statement on this however. One other possibility is that the incidence of thyrotoxicosis in people under forty has reached its permanent plateau, but the older group incidence may continue to fall slowly. In this case the overall incidence, could become less than it is at present. There has been no change in the age group structure in Southern Tasmania during the period of observation. (Bureau of Census and Statistics, Tasmania).

The mortality rate which is low at present because of radiotherapy, antithyroid drugs and good surgery should drop even lower as younger people develop the disease, and the malignant cancer of the elderly which is associated with endemic goitre, should all but disappear. Figure 11 - 3 shows that the mortality from thyrotoxicosis, increased in the days before therapy with radioiodine and good anaesthesia, fell dramatically with the introduction of antithyroid drugs. One could assume that the decrease in mortality which had remained elevated for twenty years, was due not to a decreased incidence of the disease but better treatment.

The decline in the mortality rate of thyrotoxicosis, the falling incidence of cancer in the elderly, the absence of tracheal obstruction and ugly thyroid swellings in females is paid for by a slightly increased incidence of thyrotoxicosis, a tendency unmasked by iodine in about 1 per 3000 of the population per year, and with

an incidence of cancer of papillary type in one per cent of these people, the latter having a very low mortality rate. Recent experimental work suggests a connection between pathology in the female breast including carcinoma and iodine deficiency. If this is confirmed there is a further reason for adding iodine to environments which are naturally deficient in the element (Eskin 1970).

These seem to be some of the implications of iodbasedow as I have observed it in Southern Tasmania. If iodbasedow means thyrotoxicosis in elderly goitrous females, time will see its lessening but thyrotoxicosis should remain at the present level or slightly less, which is probably equal to that of the rest of the world where iodine deficiency does not occur.

R E F E R E N C E S

- ACKERMAN, L.V. (1953): Thyroid. In Surgical Pathology, C.V. Mosby, St. Louis, 226.
- ADAMS, D.D. (1971): Personal communication.
- ADAMS, D.D., and KENNEDY, T.H. (1971): Evidence to suggest that L.A.T.S. protector stimulates the human thyroid gland, J. clin. Endocr. 33:47
- ALLCROFT, R., and SALT, F.J. (1961): Goitrogenic factors in kale (*Brassica oleracea*). In Advances in Thyroid Research, edited by Pitt-Rivers, R., Pergamon Press, London, 4.
- ANDERSON, G.M. (1914): British Medical Association News, Med. J. Aust. 1:388.
- ANDERSON, W.A.D., and WINSHIP, T. (1961): Thyroid gland. In Pathology, edited by Anderson, W.A.D., C.V. Mosby, St. Louis, 1019.
- ARSTILA, A., KRUSIUS, F.E., and PELTOLA, P. (1969): Studies on the transfer of thio-oxazolidone-type goitrogens into cow's milk in goitre endemic districts of Finland and in experimental conditions, Acta Endocr. 60:712.
- ASTWOOD, E.B. (1949): The natural occurrence of anti-thyroid compounds as a cause of simple goiter, Ann. intern. Med. 30:1087.

- ASTWOOD, E.B., GREER, M.A., and ETTLINGER, M.G. (1949): L-5-vinyl-2-thio-oxazolidone, an antithyroid compound from yellow turnip and from brassica seeds, J. biol. Chem. 181:121.
- BACHELARD, H.S., and TRIKOJUS, V.M. (1960): Plant thioglycosides and the problem of endemic goitre in Australia, Nature (Lond.), 185:80.
- BACHELARD, H.S., and TRIKOJUS, V.M. (1964): Chemical and biochemical studies on endemic goitre. In Naturally Occurring Goitrogens and Thyroid Function, edited by Podoba, J., and Langer, P., Publishing House of the Slovak Academy of Sciences, Bratislava, 57.
- BAILEY, H., and BISHOP, W.J. (1944): quoted by Langer, P. (1960): In Endemic Goitre, Wld. Hlth. Org., Monograph Series No. 44, Geneva, 9.
- BANKS, M.R. (1965): Geology of Tasmania. In Atlas of Tasmania, edited by Davies, J.L., Tasmanian Govt. Printing Office, Hobart, 12.
- BARKER, H.M. (1936): The blood cyanates in the treatment of hypertension, J. Amer. med. Ass. 106:762.

- BASTENIE, P.A. (1947): Diseases of the thyroid gland in occupied Belgium, Lancet, 252:789.
- BAUMANN, E. (1896): quoted by Garrison, F.H. (1967): In An Introduction to the History of Medicine, W.B. Saunders, Philadelphia, 695.
- BEIERWALTES, W.H., and AL-SAAD, A.A. (1966): Chromosome abnormalities in human thyroid disease, J. clin. Endocr. 26:729.
- BLUM, M., and EISENBUD, M. (1967): Reduction of thyroid irradiation from ^{131}I by potassium iodide, J. Amer. med. Ass. 200:1036.
- BLUM, M., and CHANDRA, R. (1970): Lower normal values for ^{131}I thyroid uptake not related to the ingestion of white bread, J. nucl. Med. 12:743.
- BOOTHBY, W.M. (1935): Disease of the thyroid gland: An interpretative review of progress toward solution of the problem, Arch. intern. Med. 56:136.
- BORNHAUSER, S. (1936): quoted by Langer, P. (1960): In Endemic Goitre, Wld. Hlth. Org., Monograph Series No. 44, Geneva, 9.
- BOUSSINGAULT, J.B. (1833): quoted by Marine, D. (1954): In Endemic goiter a problem in preventive medicine, Ann. intern. Med. 41:875.

- BRAY, G.A. (1968): Increased sensitivity of the thyroid in iodine-depleted rats to the goitrogenic effects of thyrotropin, J. clin. Invest. 47:1640.
- BREUER, R. (1900): quoted by Rundle, F.F. (1951): In Joll's Diseases of the Thyroid Gland, Heinemann, London, 142.
- BRUSH, B.E., and ALTLAND, J.K. (1952): Goiter prevention with iodized salt: results of 30 year study, J. clin. Endocr. 12:1380.
- BURKAT, S.E. (1965): Hygienic importance of the adsorption of iodine by humic acids, Gigiena i Sanit. 30:97.
- BURKE, G. (1970): Effects of iodide on thyroid stimulation, J. clin. Endocr. 30:76.
- BURNS, A. (1811): quoted by Garrison, F.H. (1967): In An Introduction to the History of Medicine, W.B. Saunders, Philadelphia, 486.
- BURRELL, C.D., and FRASER, R. (1957): The iodide-repletion test, Quart. J. Med. 104:559.
- BUTLER, G.W., JOHNSON, J.M., FLUX, D.S., and PETERSEN, G.B. (1956): Iodine nutrition of grazing animals, Proc. N.Z. Inst. Ag. Sc. 5:62.

- BUTTFIELD, I.H., and HETZEL, B.S. (1967): Endemic goitre in eastern New Guinea with special reference to the use of iodised oil in prophylaxis and treatment, Bull. Wld. Hlth. Org. 36:243.
- BUTTFIELD, I.H., and HETZEL, B.S. (1969): Endemic goitre in New Guinea and the prophylactic program with iodinated poppy seed oil. In Endemic Goiter, Pan American Health Organization Scientific Publication No. 193, edited by Stanbury, J.B., Washington, 132.
- BUZINA, R. (1970): Ten years of goiter prophylaxis in Croatia, Yugoslavia, Amer. J. clin. Nutr. 23:1085.
- CAMPBELL, J.M.H. (1925): The geographical distribution of exophthalmic goitre in the British Isles, Quart. J. Med. 18:191.
- CARMALT-JONES, (1928): Iodine causing toxic adenoma, Proc. Roy. Soc. Med. 21:59.
- CHATIN, A. (1853): quoted by Dobyns, B. W. (1969): In Current Problems in Surgery: Goiter, Year Book Medical Publishers, Chicago, 3.
- CHEN, T.C. (1954): Endemic goitre in Taiwan, Taiwan Igakkai Zasshi. 53:593.

- CHESNEY, A.M., CLAWSON, T.A., and WEBSTER, B. (1928):
Endemic goitre in rabbits. 1. incidence and
characteristics, Bull. Johns Hopk. Hosp. 43:261
- CHOPRA, I.J., BEALL, G.N., and SOLOMON, D.H. (1971):
L.A.T.S. inhibition by a soluble lipoprotein from
human thyroid, J. clin. Endocr. 32:772.
- CHOUFOER, J.C., Van RHIJN, M., KASSENAAR, A., and
QUERIDO, A. (1963): Endemic goiter in western
New Guinea: Iodine metabolism in goitrous and
non goitrous subjects, J. clin. Endocr. 23:1203.
- CHRISTHILF, S.M. (1966): Simplified incidental
appendectomy, Surq. Gynec. Obst. 122:607.
- CLARK, T., and PIERCE, C.C. (1921): Endemic Goitre,
Reprint 184, United States Public Health Service,
Washington.
- CLEMENTS, F.W. (1949): Endemic goitre in Tasmania.
Report of a survey submitted to the Minister for
Health, Hobart, March, 1949.
- CLEMENTS, F.W. (1954): Endemic goitre in Tasmania.
Report of a survey submitted to the Minister for
Health, Hobart, March, 1954.
- CLEMENTS, F.W. (1954): The relationship of thyrotoxi-
cosis and carcinoma of the thyroid to endemic
goitre, Med. J. Aust. 2:894.

CLEMENTS, F.W. (1955): A thyroid blocking agent as a cause of endemic goitre in Tasmania, Med. J. Aust. 2:369.

CLEMENTS, F.W., and WISHART, H.W. (1956): A thyroid-blocking agent in the etiology of endemic goitre, Metabolism, 5:623.

CLEMENTS, F.W. (1958): Endemic goitre: Scope of the health problem and related conditions, Bull. Wld. Hlth. Org. 18:175.

CLEMENTS, F.W. (1960): Health significance of endemic goitre and related conditions. In Endemic Goitre, Wld. Hlth. Org., Monograph Series No. 44, Geneva, 235.

CLEMENTS, F.W., GIBSON, H.B., and HOWELER-COY, J.F. (1968): Goitre studies in Tasmania, Bull. Wld. Hlth. Org. 38:297.

CLEMENTS, F.W., and GIBSON, H.B. (1970): Goitre prophylaxis by addition of potassium iodate to bread, Lancet, 1:489.

CLUTE, H.M., and MASON, R.L. (1927): Iodin as a therapeutic aid to surgery in primary hyperthyroidism, Boston med. surg. J. 197:247.

COINDET, J.F. (1820): quoted by Dobyns, B.M. (1969):

In Current Problems in Surgery : Goiter, Year
Book Medical Publishers, Chicago, 3.

COLLER, F.A. (1926): The use of iodine in the treatment of goitre, Ann. clin. Med. 5:93.

COLLER, F.A. (1929): Adenoma and cancer of the thyroid, J. Amer. med. Ass. 92:457.

CONNOLLY, R.J., VIDOR, G., HETZEL, B.S., BUTTFIELD, I.H., STEWART, J.C., and SHERWOOD, J. (1968): Studies of thyrotoxicosis in Tasmania, Med. J. Aust. 2:742.

CONNOLLY, R.J., STEWART, J.C., and VIDOR, G. (1970): An increase in thyrotoxicosis in an endemic goitre area following iodisation of bread, Lancet, 1:500.

CONNOLLY, R.J. (1970): Seasonal variation in thyroid function, Med. J. Aust. 1:633.

CONNOLLY, R.J. (1971): An increase in thyrotoxicosis in southern Tasmania after an increase in dietary iodine, Med. J. Aust. 1:1268.

CONNOLLY, R.J. (1971): The changing iodine environment of Tasmania, Med. J. Aust. 2:1191.

CONNOLLY, R.J. (1971): Iodbasedow, Quart. J. Surg. Sc. 7:188.

- CONNOLLY, R.J., and SHEPHERD, J.J. (1972): The effect of preoperative surgical scrubbing with povidone iodine on urinary iodine levels, Aust. N.Z. J. Surg. in press.
- CORREA, P., CUELLO, C., and EISENBERG, H. (1969): Epidemiology of different types of thyroid cancer. In Thyroid Cancer, U.I.C.C. Monograph Vol. 12, edited by Hedinger, C.E., Heinemann, London, 81.
- CRAIG, C. (1963): The First Hundred Years 1863-1963, Board of Management, Launceston General Hospital, Launceston.
- CRILE, G., and DEMPSEY, W.S. (1949): Indications for removal of nontoxic nodular goiter, J. Amer. med. Ass. 139:1247.
- CRISP, M.P. (1968): Report of the Royal Commissioner into the Fluoridation of Public Water Supplies. Govt. Printer, Tasmania. 15.
- CROOKS, J., MURRAY, I.P.C., and WAYNE, E.J. (1959): Statistical methods applied to the clinical diagnosis of thyrotoxicosis, Quart. J. Med. 28:211.
- DAVIES, J.L. (1965): Landforms in Tasmania. In Atlas of Tasmania, edited by Davies, J.L., Tasmanian Govt. Printing Office, Hobart, 19.
- DAY, T.K., POWELL-JACKSON, P.R. (1972): Fluoride, water hardness and endemic goitre, Lancet, 1:1135.

DELANGE, F., THILLY, C., and ERMANS, A.M. (1968):

Iodine deficiency; a permissive condition in the development of endemic goiter, J. clin. Endocr. 28:114.

DELANGE, F., HERSHMAN, J.M., and ERMANS, A.M. (1971):

Relationship between the serum thyrotropin level, the prevalence of goiter and the pattern of iodine metabolism in Idjwi Island, J. clin. Endocr. 33:261.

DEMEESTER-MIRKINE, N., and ERMANS, A.M. (1967):

Euthyroid "hot" nodules: A physiological approach. In Thyrotoxicosis, edited by Irvine, W.J., Livingstone, Edinburgh, 68.

DE QUERVAIN, F. (1922): quoted by Matovinovic, J.,

and Ramalingaswami, V. (1960): In Endemic Goitre, Wld. Hlth. Org., Monograph Series No. 44, Geneva, 387.

DE QUERVAIN, F. (1927): The pathological physiology of endemic thyropathy. In Report of the International Conference on Goitre, Bern, 134.

DE QUERVAIN, F., and GIORDANENGO, G. (1935-37): Die

akute und subakute nicht eiterige Thyroiditis. Mitt. Grenzgel. Med. u. Chir. 44:538.

- DE SMET, M.P. (1960): Pathological anatomy of endemic goitre. In Endemic Goitre, Wld. Hlth. Org., Monograph Series No 44, Geneva, 315.
- DE SMET, M.P. (1954): Contribution à l'étude de la pathologie thyroïdienne au Congo Belge, Ann. Soc. belge. Méd. trop. 34:47.
- DINSMORE, R. (1936): quoted by Jackson, A.S., and Freeman, H.E. (1936): The effect of iodine in adenomatous goitre with special reference to toxic adenomas, J. Amer. med. Ass. 106:1261.
- DOCK, G., and LISSER, H. (1927): quoted by Rolleston, Sir Humphrey D. (1936): In The Endocrine Organs in Health and Disease with an Historical Review, Oxford University Press, London, 208.
- DONIACH, I. (1969): Correlation of thyroid cell height with sex difference in tumour induction. Discussion on carcinogenic role of T.S.H. In Thyroid Cancer, U.I.C.C. Monograph Vol. 12, edited by Hedinger, C.E., Heinemann, London, 131.
- EGGENBERGER, H. (1938): Decrease in hyperthyroidism after iodised salt, Trans. Amer. Goiter Ass. 70.
- EK, B., JOHNSSON, S., VON PORAT, B. (1963): Iodide repletion test in an endemic goiter area. Risk of iodine induced hyperthyroidism, Acta. med. scand. 173:341.

- ELSLEY, T.H. (1971): Iodophor sanitizers in the dairy, Tasmanian Journal of Agriculture, 42:319.
- ERMANS, A.M., THILLY, C., VIS, H.L., and DELANGE, F. (1969): quoted by Stanbury, J.B. (1970): In Research on endemic goiter in Latin America, Wld. Hlth. Org. Chron. 24:537.
- ESKIN, B.A. (1970): Iodine metabolism and breast cancer, Trans. N. Y. Acad. Sci. 32:911.
- FARMER, R.S.J. (1965): Population of Tasmania. In Atlas of Tasmania, edited by Davies, J.L., Tasmanian Govt. Printing Office, Hobart, 46.
- FIERRO-BENITEZ, R., PENAFIEL, W., DE GROOT, L.J., and RAMIREZ, I. (1969): Endemic goitre and endemic cretinism in the Andean region, New Engl. J. Med. 1:296.
- FIERRO-BENITEZ, R., PENAFIEL, W., DE GROOT, L.J., and RAMIREZ, I. (1969): quoted by Stanbury, J.B. (1970): In Research on endemic goiter in Latin America, Wld. Hlth. Org. Chron. 24:537.
- FLAJANI, G. (1802): quoted by Danowski, T.S., (1962): In Clinical Endocrinology Vol. II, Williams and Wilkins, Baltimore, 113.

- FLUCK, W. (1938): quoted by Lowenstein, F.W. (1960):
In Endemic Goitre, Wld. Hlth. Org., Monograph
Series No. 44, Geneva, 444.
- FOLLIS, R.H. Jr. (1958): In Deficiency Diseases,
Charles C. Thomas, Springfield, 74.
- FOLLIS, R.H. Jr. (1964): Patterns of urinary iodine
excretion in goitrous and non-goitrous areas,
Amer. J. clin. Nutr. 14:253.
- FOOTE, M.N. (1954): Of boiling oil and barbers chairs,
J. clin. Endocr. 14:1385.
- FRASER, D. (1962): In Primitive Art, Thames and
Hudson, London, 240, 271.
- FRASSON, U. (1962): Finding of malignancy in non
toxic nodular goitre in a statistical study of
1816 thyroidectomies, Acta. chir. ital. 18:171.
- FURIHATA, R., and MARUCHI, N. (1969): Epidemiological
studies on thyroid cancer in Nagano prefecture,
Japan. In Thyroid Cancer, U.I.C.C. Monograph
Vol. 12, edited by Hedinger, C.E., Heinemann,
London, 79.
- GAFFORD, F.H., SHARRY, P.M., and PITTMAN, J.A. (1971):
Effect of azodicarbonide on thyroid function,
J. clin. Endocr. 32:69.

- GAHA, J.F. (1951): Personal communication.
- GAITAN, E., WAHNER, H., CUELLO, C., CORREA, P., JUBIZ, W., and GAITAN, J.E. (1968): Endemic goiter in the Cauca Valley I. Results and limitations of twelve years of iodine prophylaxis, J. clin. Endocr. 28:1730.
- GAITAN, E., WAHNER, H., CUELLO, C., CORREA, P., JUBIZ, W., and GAITAN, J.E. (1968): Endemic goiter in the Cauca Valley II. Studies of thyroid pathophysiology, J. clin. Endocr. 29:675.
- GAITAN, E., and WAHNER, H.W. (1969): quoted by Stanbury, J.B. (1970): In Research on endemic goiter in Latin America, Wld. Hlth. Org. Chron. 24:537.
- GARRISON, F.H. (1967): An Introduction to the History of Medicine, W. B. Saunders, Philadelphia, 123, 563, 685.
- GEIGER, M. (1636): quoted by Garrison, F.H. (1967): In An Introduction to the History of Medicine, W. B. Saunders, Philadelphia, 824.
- GIBSON, H.B., HOWELER, J.F., and CLEMENTS, F.W. (1960): Seasonal epidemics of endemic goitre in Tasmania, Med. J. Aust. 1:875.

- GIBSON, H.B. (1970): Personal communication.
- GODDARD, T.H. (1963): The great dispute. In The First Hundred Years 1863-1963, edited by Craig, C., Board of Management, Launceston General Hospital, Launceston, 39.
- GOETSCH, E. (1934): Studies on thyroid disorders. VII. Correct and incorrect use of iodine in the treatment of goiter, Amer. J. Surg. 26:417.
- GOLDSCHMIDT, V.M. (1954): Geochemistry, edited by Muir, A., Clarendon Press, Oxford, 602.
- GRAVES, R.D. (1835): Clinical lectures, London Med. Surg. J. 7:516.
- GREENE, R., FARRAN, H., and GLASCOCK, R.F. (1958): Goitrogens in milk, J. Endocr. 17:272.
- GREENWALD, I. (1949): Studies of exophthalmic goiter, Bull. Hist. Med. 23:155.
- GREENWALD, I. (1968): Studies of exophthalmic goiter, J. chron. Dis. 20:251.
- GREENWALD, I. (1969): Studies of exophthalmic goiter, J. chron. Dis. 21:483.
- GREENWALD, I. (1970): Studies of exophthalmic goiter, J. chron. Dis. 22:811.

- GREER, M.A. (1956): Isolation from rutabaga seed of progoitrin, the precursor of the naturally occurring antithyroid compound, goitrin (L-5-vinyl-2-thiooxazolidone), J. Amer. chem. Soc. 78:1260.
- GREER, M.A. (1964): The natural occurrence of goitrogenic agents. In Naturally Occurring Goitrogens and Thyroid Function, edited by Podoba, J., and Langer, P., Publishing House of the Slovak Academy of Sciences, Bratislava, 85.
- GREER, M.A., and ASTWOOD, F.B. (1948): The anti-thyroid effect of certain foods in man as determined with radioactive iodine, Endocrinology, 43:105.
- GREER, M.A., and ASTWOOD, F.B. (1953): Treatment of simple goitre with thyroid, J. clin. Endocr. 13:1312.
- GREIG, W.R., BOYLE, J.A., DUNCAN, A., NICOL, J., GRAY, M., and BUCHANAN, W. (1967): Genetic and non genetic factors in simple goitre formation: evidence from a twin study, Quart. J. Med. 26:175.
- GRIESBACH, W.E., KENNEDY, T.H., and PURVES, H.D. (1941): The effect of goitrogenic diet on hypophysectomised rats, Brit. J. exp. Path. 22:249.

GUREVICH, G.P. (1962): Fertilizing soil with iodine resources as a prophylactic measure against endemic goitre, Izv. Akad. Nauk. Ser. biol. 5:791.

HAKAMA, M. (1969): Different world thyroid cancer rates. In Thyroid Cancer, U.I.C.C. Monograph Vol. 12, edited by Hedinger, C.E., Heinemann, London, 66.

HALES, I., REEVE, T., MYHILL, J., and DOWDA, K. (1969): Goitre: Seasonal fluctuations in New South Wales, Med. J. Aust. 1:378.

HARDEN, R.M., ALEXANDER, W.D., KOUTRAS, D.A., HARRISON, M.T., and WAYNE, E. (1966): Quantitative studies of iodine metabolism after long term treatment of thyrotoxicosis with antithyroid drugs, J. clin. Endocr. 26:397.

HARINGTON, C.R. (1926): Chemistry of thyroxine. 11. Constitution and synthesis of desiodothyroxine, Biochem. J. 15:300.

HARINGTON, C.R. (1933): The Thyroid Gland, its Chemistry and Physiology, Oxford University Press, London.

- HARTSOCK, C.L. (1926): Iodised salt in the prevention of goiter; is it a safe measure for general use? J. Amer. med. Ass. 86:1334.
- HASHIMOTO, H. (1912): Zur Kenntnise der Lymphomatosen . Veränderung der Schilddrüse (Struma Lymphomatosa), Arch. f. klin. Chir. 97:219.
- HENNEMAN, H.A., REINEKE, E.P., and GRIFFIN, S.A. (1964): quoted by Kilpatrick, R., and Wilson, G.M. (1964): In The Thyroid Gland Vol. 2, edited by Pitt-Rivers, R., and Trotter, W.R., Butterworths, London 94.
- HERCUS, C.E., BENSON, W.N., and CARTER, C.L. (1925): Endemic goitre in New Zealand and its relationship to the soil iodine, J. Hyg. (Lond.). 24:321.
- HERCUS, C.E., and AITKEN, H.A.A. (1933): Miscellaneous studies on the iodine and goitre problems in New Zealand, J. Hyg. (Lond.). 33:55.
- HERCUS, C.E., and PURVES, H.D. (1936): Studies on endemic and experimental goitre, J. Hyg. (Lond.). 36:182.
- HERSCHMAN, J.M., READ, D.G., BAILEY, A.L., NORMAN, V.D., and GIBSON, T.B. (1970): Effect of cold exposure on serum thyrotropin, J. clin. Endocr. 30:430.

- HETTICHE, H.O. (1956): quoted by Ramalingaswami, V.
(1958): In Endemic goiter, Fed. Proc. 17:83.
- HETZEL, B.S. (1968): The aetiology and pathogenesis of hyperthyroidism, Postgrad. med. J. 44:363.
- HETZEL, B. S. (1970): The control of iodine deficiency, Med. J. Aust. 2:615.
- HIGGINS, H.P., HAWKS, G.H., O'SULLIVAN, M., and SHAW, M. (1964): The effect of povidone-iodine (Betadine) on serum protein-bound iodine when used as a surgical preparation on intact skin, Canad. med. Ass. J. 90:1298.
- HIPPOCRATES. (400 B.C.): Treatise on Airs, Waters and Places. In The Genuine Works of Hippocrates, translated from the Greek by Francis Adams, Williams and Wilkins, Baltimore (1939), 19.
- HIPSLEY, E.H. (1956): A new method of preventing goitre in Canberra (the use of iodised salt in bread baking), Med. J. Aust. 1:532.
- HIRSCH, A. (1960): quoted by Langer, P. (1960): In Endemic Goitre, Wld. Hlth. Org., Monograph Series No 44, Geneva, 9.

HODGE, H.C., and SMITH, F.A. (1965): Biological properties of inorganic fluorides. Vol. 4. Fluorine Chemistry, edited by Simons, J. H., Academic Press, New York.

HOEFER, W. (1675): quoted by Major, R.H. (1965): In Classic Descriptions of Disease, Charles C. Thomas, Springfield, 264.

HOWELER - COY, J.F. (1968): Bread consumption in Tasmania, Food Nutr. Notes Rev. 25:16.

IBBERTSON, H.K. (1970): Personal communication.

IVERSEN, K. (1948): Temporary Rise in the Frequency of Thyrotoxicosis in Denmark 1941-1945, Rosenkilde and Dagger, Copenhagen.

JACKSON, A.S. (1924): Iodine as a cause of thyrotoxicosis with a report of eighteen cases, Lancet, 44:324.

JACKSON, A.S., and EWELL, G.H. (1930): The danger of the prolonged use of lugols sln, Am. J. Surg. 10:475.

JACKSON, A.S., and FREEMAN, H.E. (1936): The effect of iodine in adenomatous goitre with special reference to toxic adenomas, J. Amer. med. Ass. 106:1261.

- JUVENAL, SATIRE XIII, quoted by Dobyns, B.M. (1969):
In Current Problems in Surgery: Goiter, Year
Book Medical Publishers, Chicago, 3.
- KAMBAL, A. (1969): Carcinoma in solitary thyroid
nodules, Brit. J. Surg. 56:434.
- KATALYMOV, M., and CHURBANOV, V.M. (1960): The effect
of liming soil and of using fertilisers contain-
ing chlorine on iodine uptake by plants, Dokl.
Akad. Nauk. 131:1191.
- KELLY, F.C., and SNEDDEN, W.W. (1960): Prevalence
and geographical distribution of endemic goiter.
In Endemic Goitre, Wld. Hlth. Org., Monograph
Series No. 44, Geneva, 27.
- KENDALL, E.C. (1919): Isolation of the iodine com-
pound which occurs in the thyroid, J. biol.
Chem. 39:125.
- KENNEDY, T.H., and PURVES, H.D. (1941): Studies on
experimental goitre 1. The effect of brassica
seed diets on rats, Brit. J. exp. Path. 22:241.
- KHAVIN, I., and NIKOLAYEV, O. (undated): Diseases
of the Thyroid Gland, Foreign Languages Publish-
ing House, Moscow.

- KILPATRICK, R., and WILSON, G.M. (1964): Simple nontoxic goitre. In The Thyroid Gland. Vol 2, edited by Pitt-Rivers, R., and Trotter, W.R., Butterworths, London, 88.
- KIMBALL, D.P., and MARINE, D. (1918): The prevention of simple goitre in man, Arch. intern. Med. 22:41.
- KIMBALL, D.P. (1925): Induced hyperthyroidism, J. Amer. med. Ass. 85:1709.
- KIMBALL, D.P. (1928): The efficiency and safety of the prevention of goiter, J. Amer. med. Ass. 91:454.
- KING, T.W. (1836): quoted by Singer, C., and Underwood, E.A. (1962): In A Short History of Medicine, Clarendon Press, Oxford, 520.
- KOCHER, T. (1910): Ueber Iodbasedow, Arch. Klin. Chir. 92:1166.
- KOUTRAS, D.A., PAPADOPOULOS, S.N., SPONTOURIS, J., RIGOPOULIS, G.A., PHARMAKIOTIS, A.D., and MALAMOS, G. (1968): Study in village of Livadi (endemic goitre). Before and six months after iodised salt 1/25,000, J. clin. Endocr. 28:1651.

- KOUTRAS, D.A., PAPAPETROU, P.D., YATAGANAS, X., and MALAMOS, B. (1970): Dietary sources of iodine in areas with and without iodine deficiency goiter, Amer. J. clin. Nutr. 23:870.
- KRISS, J.P., GREENSPAN, F.S., CARNES, W.H., and LEW, W. (1956): Alterations in chick thyroid function induced by cobalt, Endocrinology. 59:555.
- LAMBERG, B.A., HAIKONEN, M., and HINTZE, G. (1970): Regression of endemic goitre and of changes in iodine metabolism during 10 to 15 years in the east of Finland: The role of iodine prophylaxis, Hormones (Basel). 1:85.
- LANGER, P. (1960): History of Goitre. In Endemic Goitre, Wld. Hlth. Org., Monograph Series No. 44, Geneva, 9.
- LANGER, P. (1964): Serum thiocyanate level in large sections of the population as an index of the presence of naturally occurring goitrogens in the organism. In Naturally Occurring Goitrogens and Thyroid Function, edited by Podoba, J., and Langer, P., Publishing House of the Slovak Academy of Sciences, Bratislava, 281.

- LANGFORD, J. (1965): Weather and climate of Tasmania.
In Atlas of Tasmania, edited by Davies, J.L.,
Tasmanian Govt. Printing Office, Hobart, 2.
- LAROCHE, G., and HIRSCH, M. (1960): Les troubles
thyroïdiens d'origine iodée: goitre, iode-
myxodème, iode-basedow, Presse méd. 68:2119.
- LAWALL, C.H. (1926): Four Thousand Years of
Pharmacy, Lippincott, Philadelphia, 459.
- LINDSAY, S. (1969): Papillary thyroid carcinoma
revisited. In Thyroid Cancer, U.I.C.C. Monograph
Vol. 12, edited by Hedinger, C.E., Heinemann,
London, 29.
- LOWBURY, E.H.L., LILLY, H.A., and BULL, J.P. (1964):
Disinfection of hands: Removal of transient
organisms, Brit. Med. J. 1:230.
- LU-CWEI-DJEN, and NEEDHAM, J. (1967): Records of
diseases in ancient China. In Diseases in
Antiquity, edited by Brothwell, D., and Sandison,
A.T., Charles C. Thomas, Springfield, 222.
- MAJOR, R.H. (1954): A History of Medicine, Blackwell
Scientific Publications, Oxford, 94, 278.
- MAJOR, R.H. (1965): Classic Descriptions of
Disease, Charles C. Thomas, Springfield.
258, 263, 264, 275, 282.

- MALAMOS, B., KOUTRAS, D., RIGOPOULOS, G., PAPAPETROU, P., GOUGAS, E., KELPERI, H., MORAITOPOULOS, C., DAVI, E., and LEONARDOPOULOS, J. (1971): Endemic goiter in Greece: Some new epidemiologic studies, J. clin. Endocr. 32:130.
- MARINE, D., and LENHART, C.H. (1909): Colloid glands: Their etiology and physiological significance, Bull. Johns Hopk. Hosp. 20:131.
- MARINE, D., and LENHART, C.H. (1909): Relation of iodine to the structure of human thyroids, Arch. intern. Med. 4:440.
- MARINE, D., and WILLIAMS, W.W. (1909): The relation of iodine to the structure of the thyroid gland, Arch. intern. Med. 1:349.
- MARINE, D., and KIMBALL, D.P. (1920): Prevention of simple goitre in man, Arch. intern. Med. 25:661.
- MARINE, D., BAUMANN, E.J., and CIPRA, A. (1929): Studies on simple goiter produced by cabbage and other vegetables, Proc. Soc. exp. Biol. (N.Y.). 26:822.
- MARINE, D. (1935): Pathogenesis and prevention of simple or endemic goiter, J. Amer. med. Ass. 104:2334.

- MARINE, D. (1954): Endemic goiter: A problem in preventive medicine, Ann. intern. Med. 41:875.
- MATOVINOVIC, J., KOVACIC, N., and PROSERJAK, M. (1956): quoted by Matovinovic, J., and Ramalingaswami, V. (1960): In Endemic Goitre, Wld. Hlth. Org., Monograph Series No. 44, Geneva, 385.
- MATOVINOVIC, J. (1958): Endemic goiter, Fed. Proc. 17:60.
- MATOVINOVIC, J., and RAMALINGASWAMI, V. (1960): Theory and prophylaxis of endemic goitre. In Endemic Goitre, Wld. Hlth. Org., Monograph Series No 44, Geneva, 385.
- MEANS, J.H., and LERMAN, J. (1935): The action of iodine in thyrotoxicosis, J. Amer. med. Ass. 104:969.
- MEANS, J.H., DE GROOT, L.J., and STANBURY, J.B. (1963): The Thyroid and Its Diseases, McGraw-Hill, New York, 392.
- MEULENGRACHT, E. (1945): Increasing incidence of hyperthyroidism in Denmark, Acta. med. scand. 121:446.
- MILLAR, J. (1971): Personal communication.

- MILNE, K., and GREER, M.A. (1962): Classification of the diverse actions of iodide on antithyroid effect of sulfonamides and thionamides, Proc. Soc. exp. Biol. (N.Y.). 109:174.
- MORRIS, E.S. (1923): Public Health Tasmania, Med. J. Aust. 1:539.
- MUNOZ-R, M. (1970): Goiter-inducing effect of milk, R. esp. Fisiol. 26:197.
- MURPHEY, B.E.P., and PATTEE, C.J. (1964): Determination of thyroxine utilizing the property of protein-binding, J. clin. Endocr. 24:187.
- MURRAY, G.R. (1920): The life-history of the first case of myxoedema treated by thyroid extract, Brit. Med. J. 1:359.
- MURRAY, I.P.C. (1970): Thyroid scanning with ^{131}Cs , Brit. Med. J. 4:653.
- MURRAY, M.M., RYLE, J.A., SIMPSON, B.W., and WILSON, D.C. (1948): Thyroid enlargement and other changes related to the mineral content of drinking water (with a note on goitre prophylaxis), Memor. med. Res. Counc. (Lond.). No. 18.
- McCARRISON, R. (1906): Observations on endemic goitre in the Chitral and Gilgit Valleys, Lancet, 1:1110.

McCARRISON, R. (1908): Observations on endemic cretinism in the Chitral and Gilgit Valleys, Lancet, 2:1275.

McCARRISON, R. (1927): Experiment in goitre prevention; further history of goitre at Lawrence Royal Military School, Sanawar, Punjab, India, Brit. Med. J. 1:94.

McCARRISON, R. (1931): A letter to Dr. Pern, Letters to the Editor, Med. J. Aust. 2:531.

McCARRISON, R. (1933): A paper on food and goitre, Brit. Med. J. 2:671.

McCARRISON, R. (1937): The problem of endemic goitre, Brit. Med. J. 1:29.

McCLURE, R.D. (1934): Thyroid surgery as affected by generalised use of iodised salt in endemic goitre region -- preventive surgery, Ann. Surg. 100:924.

McCULLAGH, S.F. (1963): The Huon Peninsula Endemic:
1. The effectiveness of an intramuscular depot of iodised oil in the control of endemic goitre, Med. J. Aust. 1:769.

McCULLAGH, S.F. (1963): The Huon Peninsula Endemic:
11. The effect in the female of endemic goitre on reproductive function, Med. J. Aust. 1:806.

- McCULLAGH, S.F. (1963): The Huon Peninsula Endemic:
111. The effect in the female of endemic goitre
on reproductive function, Med. J. Aust. 1:844.
- McCULLAGH, S.F. (1963): The Huon Peninsula Endemic:
1V. Endemic goitre and congenital defect, Med.
J. Aust. 1:884.
- McGIRR, E.M., and GREIG, W.R. (1968): Epidemiology
of thyroid disease, Proc. roy. Soc. Med. 61:385.
- McGIRR, E.M. (1972): The pathogenesis and treatment
of thyrotoxicosis. In Modern Trends in Endocrin-
ology, edited by Prunty, F.T.G., and Gardiner-
Hill, H., Butterworths, London, 221.
- MackENZIE, J.B., and MacKENZIE, C.G. (1942): The
effect of "sulpha" drugs on the thyroid gland
in rats and mice, Fed. Proc. 1:122.
- McKENZIE, J.M. (1961): Studies on the thyroid
activator or hyperthyroidism, J. clin. Endocr.
21:635.
- McLENDON, J.J., and WILLIAMS, A. (1922-23): Experi-
mental goiter and iodine in natural waters in
relation to distribution of goiter, Proc. Soc.
exp. Biol. (N.Y.). 20:286.
- McLENDON, J.J. (1939): Iodine and the Incidence of
Goitre, Univ. Minnesota Press, Minneapolis.

- NEWMAN, N.M. (1971): Personal communication.
- NICHOLLS, K.D. (1965): Soils of Tasmania. In Atlas of Tasmania, edited by Davies, J.L., Tasmanian Govt. Printing Office, Hobart, 27.
- ODDIE, T.H., FISHER, D.A., MCCONAHEY, W.M., and THOMPSON, C.S. (1970): Iodine intake in the United States: A reassessment, J. clin. Endocr. 30:659.
- OLEN, E., and KLINCK, G.H. (1968): Hyperthyroidism and thyroid cancer, Arch. Path. 81:531.
- ORD, W.M. (1878): On myxoedema, a term proposed to be applied to an essential condition in a "cretinoid" affection occasionally observed in middle aged women, Tr. Med-Chir. Soc. London. 61:57.
- OSMOND, A., and CLEMENTS, F.W. (1948): Goitre studies: Relationship of endemic goitre to food consumption pattern of families, Med. J. Aust. 1:665.
- OSWALD, A. (1899): quoted by Rolleston, Sir Humphrey D. (1936): In The Endocrine Organs in Health and Disease with an Historical Review, Oxford University Press, London, 153.

PARIS, J., McCONAHEY, W.M., OWEN, C.A., WODLNER, L.B., and BAHN, R.C. (1960): Iodide goiter, J. clin. Endocr. 20:57.

PARACELSUS, (1603): quoted by Major, R.H. (1965): In Classic Descriptions of Disease, Charles. C. Thomas, Springfield, 261.

PARRY, C.H. (1825): quoted by Major, R.H. (1965): In Classic Descriptions of Disease, Charles. C. Thomas, Springfield, 276.

PASMA, F. (1948): quoted by Hipsley, E. (1956): A new method of preventing goitre in Canberra (the use of iodised salt in bread baking), Med. J. Aust. 1:533.

PASTAN, I., MACCHIA, V., and KAZIN, R. (1968): Effect of fluoride on the metabolic activity of thyroid slices, Endocrinology, 84:157.

PAUWELS, B. (1961): Iodine as a micronutrient for plants, Plant and Soil, 14:377.

PEDERSEN, E., and HOUGEN, A. (1969): Thyroid cancer in Norway. In Thyroid Cancer, U.I.C.C. Monograph Vol. 12, edited by Hedinger, C.E., Heinemann, London 71.

- PELTOLA, P. (1960): Goitrogenic effect of cow's milk from the goitre district of Finland, Acta. endocr. (Kbh.). 34:121.
- PELTOLA, P. (1960): The goitrogenic effect of milk obtained from the region of endemic goitre in Finland. In Advances in Thyroid Research, edited by Pitt-Rivers, R., Pergamon Press, London, 10.
- PENDEGRAST, W.J., MILMORE, B.K., and MARCUS, S.C. (1961): Thyroid cancer and thyrotoxicosis in the United States: Their relation to endemic goitre, J. Chron. Dis. 13:22.
- PERINETTI, H. (1969): Regional differences in cancer incidence. In Thyroid Cancer, U.I.C.C. Monograph Vol. 12, edited by Hedinger, C.E., Heinemann, London, 123.
- PERINETTI, H., GINER, M., BARBETTO, A., GANGIANI, R.J., PARISII, T., PATURZO, E., and MARTINS, H. (1960): The use of iodized salt in a region suffering goiter due to the lack of iodine. In Advances in Thyroid Research, edited by Pitt-Rivers, R., Pergamon Press, London, 283.
- PERN, I. (1931): Letters to the editor, Med. J. Aust. 2:531.

PETREA, I. (1969): Iodine and thyroid cancer. In Thyroid Cancer, U.I.C.C. Monograph Vol. 12, edited by Hedinger, C.E., Heinemann, London, 124.

PIERCY, J.E. (1968): Treatment of thyroid cancer based on pathology. In Thyroid Neoplasia, edited by Stretton Young, and Inman, D.R., Academic Press, London, 97.

PITTMAN, J.A., DAILEY, G.E., and BESCHI, R.J. (1969): Changing normal values for thyroidal radioiodine uptake, New Engl. J. Med. 280:1431.

PLATTER, Felix. (1560): quoted by Major, R.H. (1965): In Classic Descriptions of Disease, Charles C. Thomas, Springfield, 263.

PLINY, the elder: quoted by Major, R.H. (1965): In Classic Descriptions of Disease, Charles C. Thomas, Springfield, 258.

PLUMMER, H.S. (1913): Clinical and pathological relationship of simple and exophthalmic goiter, Amer. J. med. Sci. 146:790.

PLUMMER, H.S. (1923): Results of administering iodine to patients having exophthalmic goiter, J. Amer. med. Ass. 80:1955.

- PLUMMER, H.S., and BOOTHBY, W.M. (1924): Value of iodine in exophthalmic goiter, J. Iowa St. med. Soc. 14:66.
- PREVOST, J.L., and MAFFONI, A.C. (1846): quoted by Langer, P. (1960): In Endemic Goitre, Wld. Hlth. Org., Monograph Series No. 44. Geneva, 9.
- PROUT, W. (1834): quoted by Dobyns, B. W., (1969): In Current Problems in Surgery: Goiter, Year Book Medical Publishers, Chicago, 3.
- PRYDE, A. (1944): Thyroidectomy, Med. J. Aust. 1:24.
- PRYDE, A. (1958): Thyroidectomy - 1000 cases, Med. J. Aust. 1:66.
- PUBLIC HEALTH REPORTS (1906): In Australasian medical gazette, 25:45.
- PUBLIC HEALTH REPORTS (1916): In Med. J. Aust. 1:38.
- PUBLIC HEALTH REPORTS (1918): In Med. J. Aust. 1:206.
- PUBLIC HEALTH REPORTS (1922): In Med. J. Aust. 1:504.
- PUBLIC HEALTH REPORTS (1930): In Med. J. Aust. 2:586.
- PURVES, H. D., and GRIESBACH, W.E. (1946): Studies in experimental goitre. VII: thyroid carcinoma in rats treated with thiourea, Brit. J. exp. Path. 27:294.

- PURVES, H.D., and GRIESBACH, W.E. (1947): Studies in experimental goitre. Vlll: thyroid tumours in rats treated with thiourea, Brit. J. exp. Path. 28:46.
- RAMALINGASWAMI. V. (1969): Iodine and thyroid cancer in man. In Thyroid Cancer, U.I.C.C. Monograph Vol. 12, edited by Hedinger, C.E., Heinemann, London, 111.
- RANDALL, W. (1970): Sunshine rhythms, a possible zeitgeber for multiphasic biological rhythms during a year, J. interdiscpl. cycle Res. 1:389.
- READ, J.M. (1939): Studies in exophthalmic goiter. 1. Its incidence throughout the United States, Arch. intern. Med. 63:71.
- REITH, J.F. (1933): Hohe tägliche zufuhr non anorganischem Jod durch holländische Leitungswässer, Biochem. ztschr. 263:395.
- RICHARD, M. (1951): Goiter endemic in northeastern Switzerland; results of 27 years of prophylaxis with iodised salt. J. Amer. med. Ass. 145:1300.

- RICORD, G. (1862): quoted by Laroche, G., and Hirsch, M. (1960): Les troubles thyroïdiens d'origine iodée: goitre, iode-myxodème, iode-basedow, Presse med. 68:2119.
- RIEDEL, H. (1896): quoted by Ackerman, L.S. (1953): Thyroid. In Surgical Pathology, C.V. Mosby, St. Louis, 256.
- RILLIET, F. (1858): quoted by Laroche, G., and Hirsch, M. (1960): Les troubles thyroïdiens d'origine iodée: goitre, iode-myxodème, iode-basedow, Presse med. 68:2119.
- ROBBINS, S.L. (1962): Thyroid gland. In Textbook of Pathology with Clinical Application, W.B. Saunders, Philadelphia, 963.
- ROCHE, J., and LISSITZKY, S. (1960): Etiology of endemic goitre. In Endemic Goitre, Wld. Hlth. Org., Monograph Series No. 44, Geneva, 351.
- ROLLESTON, Sir Humphrey D. (1936): The Endocrine Organs in Health and Disease with an Historical Review, Oxford University Press, London, 14.
- RUNDLE, F.F. (1951): The problem of simple goitre, Med. J. Aust. 2:464.

- SACHS, B.A., SIEGEL, E., HORWOTT, B.M. and SIEGEL, E. (1972): Bread iodine content and thyroid radioiodine uptake: A tale of two cities, Brit. Med. J. 1:79.
- SAINT-LAGER, J. (1867): quoted by Marine, D. (1954): In: Endemic goiter: A problem in preventive medicine, Ann. intern. Med. 41:875.
- SANDISON, A.T., and WELLS, C.P. (1967): Endocrine diseases. In Diseases in Antiquity, edited by Brothwell, D., and Sandison, A.T., Charles C. Thomas, Springfield, 521.
- SAXÉN, E. (1950): Carcinoma thyroidea and its incidence in Finland, Acta. chir. scand. Suppl. 156:1.
- SAXÉN, E., FRANSSILA, K., and HAKAMA, M. (1969): Undifferentiated carcinomas. In Thyroid Cancer, U.I.C.C. Monograph Vol. 12, edited by Hedinger, C.E., Heinemann, London, 44.
- SAYYID ISMAIL AL-JURJANI. (1136): quoted by Rolleston, Sir Humphrey D. (1936): The Endocrine Organs in Health and Disease with an Historical Review, Oxford University Press, London, 210.

SCHELENZ, H. (1910): quoted by Langer, P. (1960):

In Endemic Goitre, Wld. Hlth. Org., Monograph
Series No. 44, Geneva, 9.

SCHIFF, M. (1884): quoted by Boothby, W.M. (1935):

In Disease of the thyroid gland: An interpretative
review of progress toward solution of the problem,
Arch. intern. Med. 56:136.

SCRIMSHAW, N.S., CAHEZAS, A., CASTILLO, F., and

MENDEZ, J. (1953): Effectiveness of iodides in
controlling goitre, Lancet, 2:166.

SHELANSKI, H.A., and SHELANSKI, M.V. (1956): P.V.P.-

Iodine. History toxicity and therapeutic uses,
J. Int. coll. Surg. 25:727.

SHULPINOV, S.S. (1957): The content of iodine in the

soil and food products and its relation to the
etiology of endemic goitre, Sborn. nauch. Rabot
Kazan. gosudarst. Med. Inst. 1:5.

SIMPSON, B.W. (1930): Iodine deficiency and live

stock. A preliminary investigation in the
Wanaka area, N.Z. J. Agric. 40:226.

SOKAL, J.E. (1954): Incidence of malignancy in toxic

and non-toxic nodular goiter, J. Amer. med. Ass.
154:1321.

- SOOCH, S.S., and RAMALINGASWAMI, V. (1965): Preliminary report of an experiment in the Kangra Valley for the prevention of Himalayan endemic goitre with iodised salt, Bull. Wld. Hlth. Org. 32:299.
- STANBURY, J.B. (1953): Summary report of 1952 Wld. Hlth. Org. Conference on endemic goiter, J. clin. Endocr. 13:1270.
- STANBURY, J.B., BROWNELL, G.L., RIGGS, D.S., PERINETTI, H., ITOIZ, J., and DEL CASTILLO, E.B., (1954): Endemic Goiter: The Adaptation of Man to Iodine Deficiency, Harvard University Press, Cambridge, Mass.
- STANBURY, J.C., and QUERIDO, A. (1956): Genetic and environmental factors in cretinism, J. clin. Endocr. 16:1522.
- STANBURY, J.B. (1958): Iodine metabolism and physiological aspects of endemic goiter, Bull. Wld. Hlth. Org. 18:201.
- STANBURY, J.B. (1969): Thyroid-specific metabolic incompetence and tumour development. In Thyroid Cancer, U.I.C.C. Monograph Vol. 12, edited by Hedinger, C.E., Heinemann, London, 183.

- STANBURY, J.B. (1970): Research on endemic goiter in Latin America, Wld. Hlth. Org. Chron. 24:537.
- STATHAM, M. (1971): Personal communication.
- STATISTICS OF TASMANIA. (1968-69): Tasmanian Govt. Printing Office, Hobart.
- STERLING, K., and TABACHNICK, M. (1961): Resin uptake of I^{131} triiodothyronine as a test of thyroid function, J. clin. Endocr. 21:456.
- STEWART, J.C., VIDOR, G.I., BUTTFIELD, I.H., and HETZEL, B.S. (1971): Epidemic thyrotoxicosis in northern Tasmania, Aust. Ann. Med. 1:203.
- STEYN, D.G. (1949): Fluorine and endemic goitre, J. Amer. med. Ass. 139:549.
- STUDER, H. (1969): Opening lecture. In Thyroid Cancer, U.I.C.C. Monograph Vol. 12, edited by Hedinger, C.E., Heinemann, London, 4.
- SUTTON, H. (1927): Thyroid enlargement in Australia: Incidence, aetiology and prevention, Supplement to Med. J. Aust. 2:20.
- TASMANIAN YEAR BOOK. (1971): Tasmanian Govt. Printing Office, Hobart, 150.
- THE THYROID ADVISORY COMMITTEE. TASMANIA. (1967--).

- TWOMEY, A. (1968): Iodophors: Their physical, chemical and bactericidal properties and use in the dairy industry - a review, Aust. J. Dairy Technol. 23:162.
- VANDER, J.B., GASTON, E.A., and DAWBER, T.R. (1968): The significance of nontoxic thyroid nodules. Final report of a 15 year study of the incidence of thyroid malignancy, Ann. intern. Med. 69:537.
- VANDERLAAN, W.P. (1956): Myxoedema and goiter attributed to iodine ingestion in a patient subsequently developing hyperthyroidism, Metabolism, 5:640.
- Van LEEUWEN, E. (1954): Form of true hyperthyroidism following ingestion of iodised bread, Nederl. tidjschi. geneesk. 98:81.
- VEALL, N., and VETTER, H. (1958): Radioisotope Techniques in Clinical Research and Diagnosis, Butterworths, London, 285, 295.
- VESALIUS, A. (1543): quoted by Major, R.H. (1954): In A History of Medicine, Blackwell Scientific Publications, Oxford, 406.

VIDOR, G., HETZEL, B.S., BUTTFIELD, I.H., CONNOLLY, R.J., STEWART, J., and SHERWOOD, J. (1968): Studies of thyrotoxicosis in Tasmania, Aust. Ann. Med. 17:162.

VIDOR, G., and STEWART, J.C., (1972): Personal communication.

VINOGRADOV, A.P. (1959): The Geochemistry of Rare and Dispersed Chemical Elements in Soils, 2nd Edition, Consultants Bureau Inc., Chapman and Hall, London, 53, 55, 56, 59, 405.

VIRTANEN, A.I., KREULA, M., and KIESVAARA, M. (1959): On the transfer of L-5-vinyl-2-thiooxazolidone from the rumen to the milk, Acta. chem. scand. 13:1043.

VIRTANEN, A.I. (1961): Chemistry of brassica factors: Their effect on function of thyroid and their flow into milk, Experientia, 17:241.

VIRTANEN, A.I. (1963): Investigation on the alleged goitrogenic properties of milk, Biochemical Institute, Helsinki.

VITRUVIUS, P.M. (50 B.C.): quoted by Langer, P. (1960): In Endemic Goitre, Wld. Hlth. Org., Monograph Series No. 44, Geneva, 9.

- VON BASEDOW, C.A. (1840): quoted by Major, R.H. (1965):
In Classic Descriptions of Disease, Charles C.
Thomas, Springfield, 283.
- VON BASEDOW, C.A. (1848): quoted by Major, R.H. (1965):
In Classic Descriptions of Disease, Charles C.
Thomas, Springfield, 285.
- Von FELLEBERG, T. (1923): Untersuchlanger über das
Vorkommn von Jod in der Nature, Biochem. Z.
139:371.
- Von FELLEBERG, T., and LUNDE, G. (1926): Geochim de
l'iode, Norsk geol. tids. 9:48.
- Von FELLEBERG, T. (1926): Das vorkommn de Kreislauf
und der Stoffinechsil des Jods, Ergelin. Physiol.
25:176.
- WAHNER, H.W., MAYBERRY, W.E., GAITAN, E., and
GAITAN, J.E. (1971): Endemic goiter in the
Cauca Valley. 111. Role of serum T.S.H. in
goitrogenesis, J. clin. Endocr. 32:491.
- WALTHARD, B. (1960): The influence of iodine pro-
phylaxis of goitre on the frequency and structure
of malignant goitre. In Advances in Thyroid
Research, edited by Pitt-Rivers, R., Pergamon
Press, London, 350.

- WALTHARD, B. (1963): Changes in the form of malignant goiter with the introduction of iodine prophylaxis of the thyroid gland, Schweiz. med. Wehnschr. 93:809.
- WARREN, S., and MEISSNER, W. (1968): Tumours of the Thyroid Gland, Fascicle 4 of the Atlas of Tumour Pathology, Series 2. Armed Forces Institute of Pathology, Washington.
- WAYNE, E.J., KOUTRAS, D.A., and ALEXANDER, W.D. (1964): Clinical Aspects of Iodine Metabolism, Blackwell Scientific Publications, Oxford.
- WERNER, S.C., BOAR, S., KOUTRAS, D.A., and WAHLBERG, P. (1970): Circulating immunoglobulin M: Increased concentrations in endemic and sporadic goiter, Science, 170:1201.
- WHARTON, T. (1656): quoted by Major, R.H. (1954): In A History of Medicine, Blackwell Scientific Publications, Oxford, 555.
- WHITTINGHAM, S., and MACKAY, I.R. (1970): Auto-antibodies in patients with thyrotoxicosis in an endemic goitre area after iodation of bread, Lancet, 1:520.

- WILKE, G. (1936): quoted by Langer, P. (1960): In Endemic Goitre, Wld. Hlth. Org., Monograph Series No. 44, Geneva, 9.
- WINSHIP, T., and ROSVOLL, R.V. (1969): Papillary carcinoma of the thyroid. In Thyroid Cancer, U.I.C.C. Monograph Vol. 12, edited by Hedinger, C.E., Heinemann, London, 32.
- WOLFF, J. (1969): Iodide goiter and the pharmacologic effects of excess iodide, Amer. J. Med. 47:101.
- WOLFF, J., and VARONNE, S. (1969): The methyl xanthines - a new class of goitrogens, Endocrinology, 85:410.
- WOOLNER, L.B., BEAHRS, O.H., BLACK, B.M., MCCONAHEY, W.M., and KEATING, F.R. (1968): Thyroid carcinoma: general considerations and follow-up data on 1181 cases. In Thyroid Neoplasia, edited by Stretton Young, and Inman, D.R., Academic Press, London, 51.
- WRIGHT, E. (1958): Goitrogen of milk produced on kale, Nature (Lond.), 181:1602.
- WYNDHAM, N. (1940): Some aspects of thyrotoxicosis in New South Wales, Med. J. Aust. 1:756.